GLYCOSAMINOGLYCAN (GAG) MIMETICS

TECHNICAL FIELD

The invention that is the subject of this application lies in the area of compounds that mimic the structure of certain carbohydrates. More particularly, the invention lies in the area of glycosaminoglycan (GAG) mimetics.

Specifically, the invention relates to compounds comprising at least one charged group that are designed to mimic the structure of GAGs. The invention also relates to methods for the preparation of the compounds, compositions comprising the compounds, and use of the compounds and compositions thereof for the antiangiogenic, antimetastatic, anti-inflammatory, anticoagulant, antithrombotic, and/or antimicrobial treatment of a mammalian subject. The invention further relates to the use of the compounds and compositions thereof in the treatment of a mammalian subject having a condition amenable to treatment with such agents.

BACKGROUND ART

Glycosaminoglycans (GAGs) are linear, polyanionic polysaccharides that are produced by most animal cells and are usually found attached to a protein core [1,2]. GAGs occur abundantly (as proteoglycans) and are extruded by cells to the cell surface and into the extracellular matrix (ECM) [3]. It has been recognised that GAGs, especially those belonging to the heparan sulfate (HS) family (HS-GAGs), mediate numerous physiological processes. For example, HS-GAGs play key roles in cell growth and development, angiogenesis, coagulation, tumour metastasis, cell adhesion, activation of growth factors, binding of cytokines and chemokines, and infection by bacteria and viruses [4-6]. In recent years there has been a dramatic increase in the list of proteins that interact with GAGs and the list continues to grow. The emerging view is that unique sequences of extracellular GAGs bind specifically to important proteins and by doing so influence fundamental biological processes.

It has been shown that molecules that mimic the structure of certain GAGs—which molecules are referred to as "GAG mimetics"—can bind to GAG-binding proteins and modulate their biological activity: e.g., the activation of AT-III by various pentasaccharides [7,8], or the activation of fibroblast growth factors (FGFs) by sucrose octasulfate [9]. Similarly, it has been shown that GAG mimetics can antagonise the binding of a GAG to its target protein and in so doing inhibit that protein's biological or disease function. For example, anticancer agents that have been developed to target HS-binding angiogenic growth factors

include polysulfonated compounds [10], suramin and the related suradistas [11], and sulfated oligosaccharides [12,13].

The present invention relates to novel, small molecule GAG mimetics that bind to GAG-binding proteins and modulate their functions. The compounds incorporate at least one negatively charged group (preferably a sulfo group) to interact with the positively charged residues in the GAG-binding site of the target proteins, and also contain one or more substituents to form interactions with other protein residues in and around the above-mentioned binding site. Important and distinguishing features of the compounds described herein are that they have fewer sulfo groups and are of lower molecular weight than previously described polysulfated GAG mimetics such as the sulfated oligosaccharides [12,13]. Another important feature is that their structures are based on cyclic scaffolds (e.g., a monosaccharide) with sulfo groups and other substituents placed in specific, pre-defined orientations about the ring, thus differing significantly from the simple, randomly charged GAG mimetics described by Kisilevsky [14]. The binding of the compounds described herein to a selection of HS-binding, angiogenic growth factors is demonstrated *via* a surface plasmon resonance (SPR) solution affinity assay. Additionally, a selection of compounds are shown to inhibit the HS-mediated infection of cells and cell-to-cell spread by herpes simplex virus.

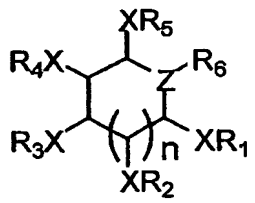
One aspect of the present invention is the utilisation of the Ugi reaction [15,16] to provide a diverse array of GAG mimetics. The capacity for variation in the manner in which the individual charged structures are connected to one another or to other functional groups as well as the scope of application to mimic the diverse structural variation of GAGs is demonstrated. As will be apparent to those skilled in the art, the functionalisation of the cyclic scaffolds is not limited to the Ugi reaction. For example, the use of many other reactions such as alkylation, acylation and cycloaddition is demonstrated.

SUMMARY OF THE INVENTION

It is an object of the invention to provide novel charged compounds that have utility as GAG mimetics.

It is a further object of the invention to provide effective synthetic routes for the preparation of the subject compounds.

According to a first embodiment of the invention, there is provided a compound of the formula



I

wherein:

n is an integer of from 0 to 2;

Z is N, N(O), O, S, S(O), $S(O)_2$, P, P(O), $P(O)_2$, Si, Si(O), or $Si(O)_2$;

each X is independently C, C(O), N, N(O), O, S, S(O), $S(O)_2$, P, P(O), $P(O)_2$, Si, Si(O), or $Si(O)_2$ or is a bond; and

each of R_1 to R_6 is independently a bond or is selected from the group consisting of:

hydrogen;

halogen;

straight chain, cyclic, branched, substituted, heterocyclic, heteroatom substituted or unsubstituted alkyl, alkenyl, alkynyl, aryl, or heteroaryl;

phosphoryl groups such as phosphate, thiophosphate -O-P(S)$(OH)_2$; phosphate esters -O-P(O)$(OR)_2$; thiophosphate esters -O-P(S)$(OR)_2$; phosphonate -O-P(O)OHR; thiophosphonate -O-P(S)OHR; substituted phosphonate -O-P(O)OR_1R_2; substituted thiophosphonate -O-P(S)OR_1R_2; -O-P(S)(OH)(SH); and cyclic phosphate;

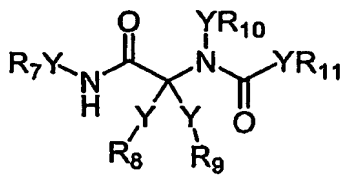
other phosphorus containing compounds such as phosphoramidite -O-P(OR)-NR_1R_2; and phosphoramidate -O-P(O)(OR)-NR_1R_2;

sulfur groups such as -O-S(O)(OH), -SH, -SR, -S(→O)-R, $S(O)_2R$, RO-$S(O)_2^-$, -O-SO_2NH_2, -O-$SO_2R_1R_2$ or sulfamide –$NHSO_2NH_2$;

amino groups such as –NHR, -NR_1R_2, -NHAc, -NHCOR, -NH-O-COR, -$NHSO_3$, -$NHSO_2R$, -$N(SO_2R)_2$, and/or amidino groups such as -NH-C(=NH)NH_2 and/or ureido groups such as -NH-CO-NR_1R_2 or thiouriedo groups such as –H-C(S)-NH_2;

another unit of the structure I, attached through any position, where Z, X and R_1 to R_6 are as defined above; or

a substructure based upon a group of the following formula:



II

wherein:

Y is a bond or is selected from the group consisting of: straight chain, cyclic, branched, substituted, heterocyclic, heteroatom substituted or unsubstituted alkyl; straight chain, cyclic, branched, substituted, heterocyclic, heteroatom substituted or unsubstituted acyl; and aryl, substituted aryl, heteroaryl;

and

each of R_7 to R_{11} is independently at least one structure according to formula **I**, or a structure according to formula **II**;

with the provisos that:

when Z is O, and X is O or a bond, then all of R_1 to R_5 are not H or CH_2OH; or

when Z is N and X is O or a bond, then all of R_1 to R_6 are not H.

According to a second embodiment of the invention, there is provided a pharmaceutical or veterinary composition for the prevention or treatment in a mammalian subject of a disorder resulting from angiogenesis, metastasis, inflammation, coagulation, thrombosis, and/or microbial infection, which composition comprises at least one compound according to the first embodiment together with a pharmaceutically or veterinarially acceptable carrier or diluent for said at least one compound.

According to a third embodiment of the invention, there is provided the use of a compound according to the first embodiment in the manufacture of a medicament for the prevention or treatment in a mammalian subject of a disorder resulting from angiogenesis, metastasis, inflammation, coagulation, thrombosis, and/or microbial infection.

According to a fourth embodiment of the invention there is provided a method for the prevention or treatment in a mammalian subject of a disorder resulting from angiogenesis, metastasis, inflammation, coagulation, thrombosis, and/or microbial infection, which method comprises administering to the subject an effective amount of at least one compound according to the first embodiment, or a composition comprising said at least one compound.

In other embodiments of the invention, there are provided processes for synthesising the compounds according to the first embodimrent as defined above.

With further regard to the compounds of the first embodiment, if not otherwise specified, alkyl, aryl and other substituent groups are used in accordance with their usual meaning in the art. For example, alkyl and aryl groups would normally have from 1 to 10 carbon atoms. Additionally, two of the groups R_1 to R_5 may be connected to each other to form a bicyclic strucure; or the cyclic structure of formula I may contain a double bond, i.e., two contiguous XR_1 to XR_5 groups may be bonds.

Preferred compounds of the invention have the general structures of formulae III–VI, as defined in Tables 1–4 below.

In order that the invention may be more readily understood and put into practice, one or more preferred embodiments thereof will now be described, by way of example only.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The following abbreviations are used herein:

GAG	glycosaminoglycan
HS	heparan sulfate
FGF	fibroblast growth factor
aFGF	acidic fibroblast growth factor (or FGF-1)
bFGF	basic fibroblast growth factor (or FGF-2)
VEGF	vascular endothelial growth factor
SPR	surface plasmon resonance
HSV	herpes simplex virus

The present inventors have found that a broad range of compounds with GAG mimetic properties can be synthesised using a number of different strategies as illustrated below in the examples. These compounds have utility in the prevention or treatment in mammalian subjects of a disorder resulting from angiogenesis, metastasis, inflammation, microbial infections, coagulation or thrombosis. This utility results from the ability of the compounds to modulate the activity of GAG-binding proteins responsible for disease processes.

The GAG mimetics of the invention, as indicated above, can be synthesised using a number of different routes, including the Ugi reaction, and generally incorporating sulfonation in the process.

Preferred compounds according to the first embodiment of the invention as defined above include those embraced by generic structures I and II and those included in Tables 1-4 below.

As indicated above, the compounds according to the invention have utility in the prevention or treatment in mammalian subjects of a disorder resulting from angiogenesis, metastasis, inflammation, microbial infection, coagulation or thrombosis. The compounds have particular utility in the treatment of the foregoing disorders in humans. The compounds are typically administered as a component of a pharmaceutical composition as described in the following paragraphs.

Pharmaceutical compositions for oral administration can be in tablet, capsule, powder or liquid form. A tablet can include a solid carrier such as gelatine or an adjuvant or an inert diluent. Liquid pharmaceutical compositions generally include a liquid carrier such as water, petroleum, animal or vegetable oils, a mineral oil or a synthetic oil. Physiological saline solution, or glycols such as ethylene glycol, propylene glycol or polyethylene glycol may be included. Such compositions and preparations will generally contain at least 0.1 wt% of the compound.

Parenteral administration includes administration by the following routes: intravenously, cutaneously or subcutaneously, nasally, intramuscularly, intraocularly, transepithelially, intraperitoneally and topically. Topical administration includes dermal, ocular, rectal, nasal, as well as administration by inhalation or by aerosol means. For intravenous, cutaneous or subcutaneous injection, or injection at a site where treatment is desired, the active ingredient will be in the form of a parenterally acceptable aqueous solution which is pyrogen-free and has suitable pH, isotonicity and stability. Those of skill in the art will be well able to prepare suitable solutions using, for example, solutions of the subject compounds or derivatives thereof.

In addition to the at least one compound and a carrier or diluent, compositions according to the invention can further include a pharmaceutically or veterinarially acceptable excipient, buffer, stabiliser, isotonicising agent, preservative or antioxidant or any other material known to those of skill in the art. It will be appreciated by the person of skill that such materials should be non-toxic and should not interfere with the efficacy of the compound(s). The precise nature of any additive may depend on the route of administration of the composition: that is, whether the composition is to be administered orally or parenterally. With regard to buffers, aqueous compositions typically include such substances so as to maintain the composition at a close to physiological pH or at least within a range of about pH 5.0 to about pH 8.0.

Compositions according to the invention can also include active ingredients in addition to the at least one compound. Such ingredients will be principally chosen for their efficacy as antiangiogenic, antimetastatic, anti-inflammatory, anticoagulant, antithrombotic, antimicrobial agents but can be chosen for their efficacy against any associated condition.

A pharmaceutical or veterinary composition according to the invention will be administered to a subject in either a prophylactically effective or a therapeutically effective amount as necessary for the particular situation under consideration. The actual amount of at least one compound administered by way of a composition, and rate and time-course of administration, will depend on the nature and severity of the condition being treated or the prophylaxis required. Prescription of treatment such as decisions on dosage and the like will be within the skill of the medical practitioner or veterinarian responsible for the care of the subject. Typically however, compositions for administration to a human subject will include between about 0.01 and 100 mg of the compound per kg of body weight and more preferably between about 0.1 and 10 mg/kg of body weight.

The compounds can be included in compositions as pharmaceutically or veterinarially acceptable derivatives thereof. As used herein "derivatives" of the compounds includes salts, coordination complexes with metal irons such as Mn^{2+} and Zn^{2+}, esters such as *in vivo* hydrolysable esters, free acids or bases, hydrates, or prodrugs. Compounds having acidic groups such as phosphates or sulfates can form salts with alkaline or alkaline earth metals such as Na, K, Mg and Ca, and with organic amines such as triethylamine and Tris (2-hydroxyethyl) amine. Salts can also be formed between compounds with basic groups, such as amines, with inorganic acids such as hydrochloric acid, phosphoric acid or sulfuric acid, or organic acids such as acetic acid, citric acid, benzoic acid, fumaric acid, or tartaric acid. Compounds having both acidic and basic groups can form internal salts.

Esters can be formed between hydroxyl or carboxylic acid groups present in the compound and an appropriate carboxylic acid or alcohol reaction partner, using techniques that will be well known to those of skill in the art.

Prodrug derivatives of the compounds of the invention can be transformed *in vivo* or *in vitro* into the parent compounds. Typically, at least one of the biological activities of a parent compound may be suppressed in the prodrug form of the compound, and can be activated by conversion of the prodrug to the parent compound or a metabolite thereof. Examples of prodrugs are glycolipid derivatives in which one or more lipid moieties are provided as substituents on the moieties, leading to the release of the free form of the compound by

cleavage with an enzyme having phospholipase activity. Prodrugs of compounds of the invention include the use of protecting groups which may be removed *in vivo* to release the active compound or serve to inhibit clearance of the drug. Suitable protecting groups will be known to those of skill in the art and include an acetate group.

As also indicated above, compounds according to the invention have utility in the manufacture of a medicament for the prevention or treatment in a mammalian subject of a disorder resulting from angiogenesis, metastasis, inflammation, coagulation, thrombosis and/or microbial infection. Processes for the manufacture of such medicaments will be known to those of skill in the art and include the processes used to manufacture the pharmaceutical compositions described above.

The compounds falling within the scope of the invention have been found to have bind growth factors. In particular, it has been established that the compounds have affinity for aFGF, bFGF and VEGF. The compounds thus have utility as antiangiogenic, antimetastatic and/or anti-inflammatory agents in the treatment of mammalian subjects including humans. The uses of the compounds include the treatment of angiogenesis-dependent diseases such as angiogenesis associated with the growth of solid tumours, and proliferative retinopathies, as well as the treatment of inflammatory diseases and conditions such as rheumatoid arthritis. The compounds may also activate the growth factors and could thus be used in cardiovascular treatments.

As further indicated above, the compounds of the invention additionally have utility as anticoagulant or antithrombotic agents. The compounds can therefore be used for both the prophylaxis and treatment of many thrombotic and cardiovascular diseases, the most notable of these being deep venous thrombosis, pulmonary embolism, thrombotic stroke, peripheral arterial thrombosis, unstable angina and myocardial infarction. Since compositions of the charged aminoacid compounds can be delivered orally, the compounds are an attractive alternative to warfarin, a widely used oral anticoagulant with severe side effects.

The compounds of the invention additonally have been found to inhibit viral infection and thus have utility as antiviral agents in the treatment or prevention of many viral infections. The compounds of the invention are particularly suited for the treatment or prevention of infection resulting from pathogens which utilise HS as an attachment/entry receptor [6], for example, HSV, HIV, Dengue virus, Yellow fever virus, Cytomegalovirus and Hepatitis C virus. Similarly, the compounds of the invention are also suited for the treatment or prevention of infection resulting from non-viral microbial pathogens which utilise HS as an

attachment/entry, for example, Plasmodium (malaria). Most notable is the inhibition by the compounds of the invention of the cell-to-cell spread of HSV-1 and HSV-2.

Having broadly described the invention, non-limiting examples of the compounds, their synthesis, and their biological activities, will now be given with reference to the accompanying Tables which will be briefly described in the following section of this specification.

General Procedures

General procedure for alkylation and deprotection of diols

The diol (1 eq.) in DMF was added dropwise to a cooled (0°), stirred suspension of pre-washed (hexane) NaH (5 eq.) in DMF. Once the addition was complete, stirring was maintained (0°→r.t., 20 min). The mixture was cooled (0°, 5 min) and the alkyl halide (2 eq.) was introduced dropwise with continued stirring (0°→r.t., o/n). The mixture was cooled once again (0°) and MeOH (5 mL) was introduced with continued stirring (5 min). The solvent was evaporated and the residue subjected to workup (EtOAc) and flash chromatography to homogeneity (TLC). This residue was co-evaporated (2 × 10 mL MeCN). The crude mixture and *p*-TsOH·H_2O (50 mg) in MeOH/MeCN (1:1) was heated under reflux (1 h). The mixture was cooled (r.t.) and Et_3N (100 μL) was added prior to evaporation of the solvent. The residue was subjected to flash chromatography (EtOAc/hexane) to yield the diol.

General procedure for sulfonation of alcohols

A mixture of the alcohol and SO_3·trimethylamine (2 eq per hydroxyl group) in DMF was heated (60°, o/n). The cooled (r.t.) reaction mixture was treated with MeOH and then made basic (to pH>10) by the addition of Na_2CO_3 (10% w/w). The mixture was filtered and the filtrate evaporated and co-evaporated (H_2O). Where deacylation of the sulfated product was required, the crude product was taken up in water and 1M NaOH was added (2 eq per acyl group). When deprotection was complete the product was carried through to the next stage. The crude sulfated material in H_2O was subjected to size exclusion chromatography. The pure fractions were evaporated and co-evaporated (H_2O) and then lyophilised (H_2O) to yield the sulfated product. When required, after lyophilisation the product was passed through an ion-exchange resin column (AG®-50W-X8, Na^+ form, 1×4 cm, deionized H_2O, 15 mL) in order to transfer the product uniformly into the sodium salt form. The solution collected was evaporated and lyophilised to give the final product as a colourless glass or white power.

Size exclusion chromatography

Size exclusion chromatography (SEC) was performed over Bio-Gel P-2 in a 5 × 100 cm column with a flow rate of 2.8 mL/min of 0.1 M NH_4HCO_3, collecting 2.8 min (7.8 mL)

fractions. Fractions were analysed for carbohydrate content by TLC (charring) and/or for poly-charged species by the dimethyl methylene blue test, and then for purity by capillary electrophoresis (CE) and those deemed to be free of salt were pooled and lyophilised.

In the cases of the presence of undersulfated by-products or other salt contaminants (normally only small amounts, but often detected), an LH20 SEC step (2 × 95 cm, deionized water, 1.2 mL/min, 3.5 min per vial) was applied to remove them completely.

Dimethyl methylene blue Test

Dimethyl methylene blue (DMB) reagent was prepared by dissolving 16 mg of DMB in 1 L of deionized water containing 3.04 g of glycine, 2.37 g of NaCl. 0.1 M HCl (95 ml) was added to adjust the pH to 3.0. The stock solution was stored in a brown coloured bottle at r.t. (the solution was stable for at least 3 months under such conditions).

A 96-well microtitre plate was loaded with 10 μL of fraction solution per well. 55 μL of DMB stock solution was added into each used well. An instant colour change from blue to pink indicated the presence of polycharged species, i.e., sulfated product fractions.

General procedure for NIS glycosylations

Glycosyl acceptor (1 eq), thioglycoside donor (1.1 eq), 500 mg of freshly activated powdered 3Å molecular sieves and 10 mL of dry DCM were stirred at -20° for 20 min before 1.3 eq of NIS and 1 drop of TfOH were added. Stirring was continued at -20° until the reaction was complete by TLC (~1 h) before 400 μL of Et_3N was added. Evaporation (*in vacuo*) onto silica gel and flash chromatography yielded the glycosylated product.

General procedure for Ugi four-component reaction

Solutions of the acid (1 eq), amine (1 eq), carbonyl compound (1 eq) and isocyanide (1 eq) in MeOH, MeOH-THF (varied ratios) or $CHCl_3$ were transferred into a reaction vial (final concentration: 0.1-0.5 M). When D-glucuronic acid was the acid component, it was added as a solid. In the case of bis-acid, bis-amine, bis-aldehyde or bis-isocyanide, the amount was 0.5 eq. The mixture was stirred or shaken at r.t. or 60 °C for 1 h to 5 days. The progress of the reaction was monitored by TLC. The mixture was evaporated and the residue was purified by flash chromatography or dried completely under high vacuum followed by direct peracetylation and purification by flash chromatography.

General procedure for acetylation of hydroxyl groups:

The corresponding alcohol was dissolved in DCM-pyridine (15:1 v/v, 0.15 M) containing DMAP (0.42 mol%). Acetic anhydride (2 eq per hydroxyl) was added and the mixture was stirred at r.t. o/n. The mixture was poured into ice-chilled 0.5 M HCl and

extracted with $CHCl_3$. The organic phase was separated and washed with cold 0.5 M HCl (×2), brine, and dried ($MgSO_4$). The solution was filtered and evaporated. The residue was purified by flash chromatography (gradient elution with hexane-EtOAc) to give pure product.

General procedure for Zemplén deacetylation/debenzoylation:

A solution of the acetate/benzoate in anhydrous MeOH (0.1 M) was treated with a solution of sodium methoxide in MeOH (1.35 M, 0.2-0.6 eq). The mixture was stirred at r.t. for 1-3 h (monitored by TLC). Acidic resin AG®-50W-X8 (H^+ form) was added to adjust the pH to 6-7, the mixture was filtered and the resin was rinsed with MeOH. The combined filtrate and washings were evaporated *in vacuo* and thoroughly dried to give the poly-ol product.

General procedure for deprotection of benzyl ethers via hydrogenolysis

To a solution of the benzyl ether-protected compound (0.03 mmol) in MeOH or EtOH (2 mL) was added 5% Pd/C or 20% $Pd(OH)_2$ on charcoal (30 mg or excess). The mixture was loaded in a miniclave (Büchi AG, Uster/Switzerland) and stirred under hydrogen atmosphere (50 psi) for 2-10 h. Alternatively, the mixture was bubbled with hydrogen gas for 1 h then stirred at r.t. under 1 atmosphere of hydrogen for 1-5 days. The reaction was monitored by TLC (EtOAc or MeCN-water 10:1). The mixture was filtered and rinsed with MeOH, or EtOH. The filtrate was evaporated and dried under high vacuum, checked by ^1H NMR, freeze-dried and used directly for sulfonation.

Methylation of hydroxyl groups

The dried poly-ol was dissolved in anhydrous DMF (0.04 M) under argon and stirred with NaH (60% suspension in mineral oil, 1.2 eq per hydroxyl) at r.t. for 1 h. Iodomethane (1.2 eq per hydroxyl) was added and stirring continued o/n. MeOH was added and the mixture was evaporated onto silica and purified by flash chromatography.

General procedure for Huisgen cycloaddition reactions.

The sulfated sugar azide was dissolved in water (0.75 M) and a solution of acetylene in *t*-butanol (0.9 M, 1 eq) was added. To this mixture was added a solution of copper (II) sulfate (0.3 M in water, 5 mol%) and a solution of sodium ascorbate (1 M, in water, 20 mol%). The mixture was shaken on a minishaker at r.t. o/n, and purified by column chromatography (silica 1x18 cm, gradient elution with EtOAc-MeOH-H_2O 50:2:1, 20:2:1 to 10:2:1) to give the corresponding triazole product.

Example 1: PG2038

Step a: Methyl 3,4,6-tri-O-acetyl-2-O-benzyl-α-D-galactopyranosyl-(1→4)-2,3,6-tri-O-benzyl-β-D-glucopyranoside.

Methyl 2,3,6-tri-O-benzyl-β-D-glucopyranoside [17] (150 mg, 322 μmol), *methyl 3,4,6-tri-O-acetyl-2-O-benzyl-1-thio-β-D-galactopyranoside* [18] (151 mg, 354 μmol) and 200 mg of 3Å molecular sieves were subjected to the general NIS glycosylation procedure using 95 mg (422 μmol) of NIS. Flash chromatography (gradient elution 20:80 to 25:75 EtOAc:hexanes) yielded 274 mg of partially deacetylated material. To this mixture was added 10 mL of DCM, 200 μL of acetic anhydride, 200 of μL Et_3N and 2 mg of DMAP, and the solution was stirred for 1 h before evaporation and flash chromatography (gradient elution 25:75 to 30:70 EtOAc:hexanes) to give 180 mg (66%) of the title compound as a colourless glass. ^{1}H n.m.r. (400 MHz, $CDCl_3$) δ: 7.05-7.35 (m, 20H, 4×Ph), 5.74 (d, 1H, $J_{1,2}$ = 4.0, H1^{II}), 5.29 (dd, 1H, $J_{3,4}$ = 3.2, $J_{4,5}$ = 1.2, H4^{II}), 5.23 (dd, 1H, $J_{2,3}$ = 10.8, H3^{II}), 4.92 (d, 1H, J_{gem} = 12.0, $PhCH_2$), 4.85 (d, 1H, J_{gem} = 10.8, $PhCH_2$), 4.55-4.69 (m, 4H, $PhCH_2$), 4.42 (AB, 1H, J_{gem} = 12.0, $PhCH_2$), 4.40 (AB, 1H, $PhCH_2$), 4.32 (d, 1H, $J_{1,2}$ = 7.6, H1^{I}), 4.10 (dt, 1H, $J_{5,6}$ = 6.8, H5^{II}), 3.88-3.96 (m, H, H5^{I}+H6^{I}), 3.82 (dd, 1H, J_{gem} = 11.1, H6^{II}), 3.70-3.76 (m, 4H, H2×H6^{I}+H2^{II}+H3^{I}), 3.56 (s, 3H, OMe), 3.5-3.6 (m, 1H, H4^{I}), 3.45 (dd, 1H, $J_{2,3}$ = 9.0, H2^{I}), 2.02 (s, 3H, Ac), 1.93 (s, 3H, Ac), 1.88 (s, 3H, Ac). ^{13}C n.m.r. (100 MHz, $CDCl_3$) δ: 170.17, 170.06, 169.87, 138.82, 138.20, 138.13, 137.68, 128.33, 128.25, 128.19, 128.04, 127.61, 127.57, 127.49, 127.46, 127.01, 126.39, 104.42, 97.12, 84.49, 82.26, 74.46, 74.27, 73.69, 73.31, 73.28, 73.02, 69.47, 69.17, 68.35, 66.60, 61.62, 56.96, 20.69, 20.63, 20.58.

Step b: Methyl 3,4,6-tri-O-acetyl-α-D-galactopyranosyl-(1→4)-β-D-glucopyranoside.

Pearlman's catalyst (20 mg) and 20 μL of acetic acid were added to a solution of 90 mg (106 μmol) of *methyl 3,4,6-tri-O-acetyl-2-O-benzyl-α-D-galactopyranosyl-(1→4)-2,3,6-tri-O-benzyl-β-D-glucopyranoside* in 10 mL of MeOH. An atmosphere of hydrogen was applied with 3 vacuum purges and the suspension was stirred for 3 days. After filtration, evaporation and co-evaporation with PhMe the residue was subjected to flash chromatography (gradient elution 100:0 to 100:3 EtOAc:MeH) to yield 47 mg (91%) of the title compound. ^{1}H n.m.r. (400 MHz, CD_3OD) δ: 5.39 (br d, 1H, $J_{3,4}$ = 3.0, H4^{II}), 5.32 (d, 1H, $J_{1,2}$ = 3.8, H1^{II}), 5.10 (dd, 1H, $J_{2,3}$ = 10.6, H3^{II}), 4.38 (br t, 1H, $J_{5,6}$ = 6.8, H5^{II}), 4.20 (d, 1H, $J_{1,2}$ = 7.8, H1^{I}), 4.09 (app d (ABX), 2H, $J_{5,6}$ = 6.5, H6^{II}), 4.00 (dd, 1H, H2^{II}), 3.92 (dd, 1H, $J_{5,6A}$ = 1.7, J_{gem} = 12.2, H6A^{I}), 3.80 (dd, 1H, $J_{5,6B}$ = 4.8, H6B^{I}), 3.62 (dis t, 1H, $J_{2,3=3,4}$ = 9.1, H3^{I}), 3.56 (part obs t, 1H, $J_{3,4=4,5}$ =

9.3, H4^{I}), 3.53 (s, 3H, OMe), 3.42 (ddd, 1H, $J_{4,5}$ = 9.4, H5^{I}), 3.22 (dd, 1H, $J_{2,3}$ = 9.1, H2^{I}), 2.10 (s, 3H, AcO), 2.05 (s, 3H, AcO), 2.00 (s, 3H, AcO).

Step c: Methyl 2-O-sulfo-α-D-galactopyranosyl-(1→4)-2,3,6-tri-O-sulfo-β-D-glucopyranoside, tetrasodium salt (PG2038)

The above disaccharide (32.2 mg, 0.667 mmol), was subjected to the standard sulfonation and deacetylation procedures to give the title compound as a white foam (4.0 mg, 7.8%, 96% purity, CE: 7.18 min). ^{1}H NMR (D_2O, 400 MHz): 5.473 (d, 1H, $J_{1II-2II}$ = 3.6, H1^{II}), 4.833 (d, 1H, J_{1I-2I} = 2.8, H1^{I}), 4.60 (overlapped with water, 1H, H3^{I}), 4.551 (m, 1H, H2^{I}), 4.306 (dd, 1H, $J_{2II-3II}$ = 10.2, H2^{II}), 4.17-4.06 (m, 4H, H4^{I}, H5^{I} and H6^{I}), 3.902 (d, 1H, $J_{3II-4II}$ = 3.6, H4^{II}), 3.867 (dd, 1H, H3^{II}), 3.616 (dd, 1H, $J_{6axII-6eqII}$ = 12.0, $J_{5II-6axII}$ = 7.2, H6ax^{II}), 3.564 (dd, 1H, $J_{5II-6eqII}$ = 5.2, H6eq^{II}), 3.363 (dd, 1H, H5^{II}), 3.343 (s, 3H, CH_3O).

Example 2: PG2046 and PG2047

Step a: 2-Azido-3,4,6-tri-O-benzoyl-2-deoxy-α-D-glucopyranosyl-(1→4)-1,6-anhydro-2-azido-2-deoxy-3-O-benzyl-β-D-glucopyranose

A solution of *3,4,6-tri-O-acetyl-2-azido-2-deoxy-D-glucopyranosyl trichloro-acetimidate* [19] (201 mg, 0.453 mmol) and *1,6-anhydro-2-azido-3-O-benzyl-2-deoxy-β-D-glucopyranose* [20] (84 mg, 0.302 mmol) in 1,2-DCE (5 mL) was stirred in the presence of activated mol. sieves (300 mg of 3Å powder) under an atmosphere of argon (r.t., 30 min). The mixture was cooled (–20°) with continued stirring (10 min) and TBDMSOTf (21 μL, 0.091 mmol) was introduced drop-wise and stirring maintained (–20°, 10 min). Et_3N (100 μL) was introduced and the mixture filtered and evaporated. The residue was subjected to aqueous workup (EtOAc) and flash chromatography (10-40% EtOAc/hexanes) to yield a pale yellow coloured oil (130 mg). This residue was co-evaporated (2 × 10 mL MeCN) then subjected to the Zemplén deacetylation general procedure. The product was subjected to aqueous workup (EtOAc) to yield a colourless oil (98 mg). This residue was co-evaporated (2 × 10 mL MeCN). BzCl (210 μL, 1.81 mmol) was added to a solution of the crude product (0.302 mmol, max.) and pyridine (2 mL) in 1,2-DCE (3 mL) and the combined mixture stirred (r.t., o/n). The mixture was cooled (0°) and MeOH (2 mL) was introduced with continued stirring (0°→r.t., 2 min) before evaporation and co-evaporation (toluene) of the solvent. The residue was subjected to aqueous workup (EtOAc) and flash chromatography (10-30% EtOAc/hexanes) to yield two compounds.

Firstly, the title compound as a colourless foam (101 mg, 46%, 3 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.11 (s, 1 H; H-2^{I}), 3.41 (dd, 1 H, $J_{1,2}$ 3.7, $J_{2,3}$ 10.7 Hz; H-6^{I}), 3.61 (s, 1 H; H-

3^{I}), 3.39 (s, 1 H; H-4^{I}), 4.05 (d, 1 H, $J_{6,6}$ 7.3 Hz; H-6^{I}), 4.41-4.49 (m, 2 H; H-6^{II}), 4.55, 4.68 (AB quartet, $J_{A,B}$ 11.9 Hz; CH_2Ph), 4.79 (ddd, 1 H, $J_{4,5}$ 10.3, $J_{5,6}$ 2.9, 5.9 Hz; H-5^{II}), 4.91 (br d, 1 H, $J_{5,6}$ 5.5 Hz; H-5^{I}), 5.08 (d, 1 H, $J_{1,2}$ 3.6 Hz; H-1^{II}), 5.51 (dd, 1 H, $J_{3,4}$ 9.5, $J_{4,5}$ 10.2 Hz, H-4^{II}), 5.60 (s, 1 H,; H-1^{I}), 6.10 (dd, 1 H, $J_{2,3}$ 10.7, $J_{3,4}$ 9.3 Hz; H-3^{II}), 7.29-7.55, 7.89-8.03 (2 m, 20 H; ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 58.74, 61.47, 63.30, 64.84, 69.19, 69.49, 70.52, 73.17, 74.62, 78.12, 79.57 (11 C; C-2^{I}-6^{I}, C2^{II}-6^{II}, CH_2Ph), 100.71, 101.16 (2 C; C-1^{I}, C-1^{II}), 128.10, 128.42, 128.57, 128.61, 128.64, 128.81, 128.88, 129.15, 129.86, 129.90, 130.06, 130.17, 133.43, 133.53, 133.74, 137.48 (Ar), 165.61, 165.62, 166.26 (3 C; C=O).

Next, *2-azido-3,4,6-tri-*O*-benzoyl-2-deoxy-*β-D*-glucopyranosyl-(1→4)-1,6-anhydro-2-azido-2-deoxy-3-*O*-benzyl-*β-D*-glucopyranose* as a colourless oil (27 mg, 12%, 3 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.19 (s, 1 H; H-2^{I}), 3.74 (dd, 1 H, $J_{5,6}$ 6.2, $J_{6,6}$ 7.1 Hz; H-6^{I}), 3.79-3.88 (m, 2 H; H-2^{II}, H-3^{I}), 3.88 (ddd, $J_{4,5}$ 9.2, $J_{5,6}$ 3.1, 4.7 Hz; H-5^{II}), 3.95 (br s, 1 H; H-4^{I}), 4.10 (d, 1 H, $J_{6,6}$ 7.3 Hz; H-6^{I}), 4.34 (dd, 1 H; $J_{5,6}$ 4.9, $J_{6,6}$ 12.2 Hz; H-6^{II}), 4.50 (dd, 1 H, $J_{5,6}$ 3.1, $J_{6,6}$ 12.3 Hz, H-6^{II}), 4.52, 4.59 (AB quartet, $J_{A,B}$ 12.0 Hz; CH_2Ph), 4.65 (d, 1 H, $J_{1,2}$ 7.9 Hz; H-1^{II}), 4.69 (br d, 1 H, $J_{5,6}$ 5.5 Hz; H-5^{I}), 5.44 (t, 1 H, $J_{2,3=3,4}$ 9.7 Hz; H-3^{II}), 5.49 (br s, 1 H; H-1^{I}), 5.51 (t, 1 H, $J_{3,4=4,5}$ 9.6 Hz; H-4^{II}), 7.23-7.50, 7.84-7.96 (2 m, 20 H; ArH).

*Step b: 2-Deoxy-2-sulfamido-*α*-D-glucopyranosyl-(1→4)-1,6-anhydro-2-deoxy-2-sulfamido-3-*O*-benzyl-*β*-D-glucopyranose, disodium salt (PG2046)*

A mixture of *2-azido-3,4,6-tri-*O*-benzoyl-2-deoxy-*α*-D-glucopyranosyl-(1→4)-1,6-anhydro-2-azido-2-deoxy-3-*O*-benzyl-*β*-D-glucopyranoside* (127 μmol), Pearlman's catalyst (11 mg), and ammonium formate (300 mg) in 2:1 MeOH:EtOAc (7 mL) was heated to 65° under argon until complete by TLC. The mixture was cooled to r.t., filtered (0.2 μm) and evaporated. The crude amine was purified by SPE (300 mg C18 Waters cartridge, equilibrated with 5:95 MeOH:H_2O, gradient eluted 5:95 to 100:0 MeOH:H_2O) to yield 53 mg of the diamine (58%). Without further purification, to the diamine was added DMF (5 mL), SO_3•Me_3N (41 mg, 295 μmol) and $NaHCO_3$ (40 mg, 475 μmol). The mixture was heated to 60° for 1 h then cooled to rt and quenched with ice and Na_2CO_3 (sat. aqueous). This suspension was stored at -18° o/n and the sample was filtered. The filtrate was evaporated. Water (1 mL) and NaOH (250 μL, 1M) were added and the solution was stirred overnight then loaded directly onto the SEC column (general procedures) to yield 22 mg (28 % over three steps) of the title compound. ^{1}H NMR (400 MHz, D_2O, solvent suppressed) δ: 7.35-7.21 (m, 5H, ArH),

5.43 (br s, 1H, $H1^{I}$), 5.18 (d, 1H, J_{1-2} = 3.6, $H1^{II}$), 4.72-4.69[1] (m, 1H, $H5^{I}$), 4.54-4.52[1] (m, 2H, $ArCH_2$), 4.05 (d, 1H, J_{gem} = 7.9, $H6A^{I}$), 3.85 (br s, 1H, $H3^{I}$), 3.76-3.58 (m, 5H), 3.51 (dd, 1H, J_{2-3} = 10.4, J_{3-4} = 9.1, $H3^{II}$), 3.34 (t, 1H, $J_{3-4-4-5}$ = 9.2, $H4^{II}$), 3.23 (br s, 1H, $H2^{I}$), 3.12 (dd, 1H, $H2^{II}$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 133.3, 124.8, 124.6, 124.4, 96.9, 95.1, 72.7, 71.5, 70.8, 68.3, 68.2, 67.2, 66.0, 61.0, 56.6, 54.0, 49.8.

Step c: 2-Deoxy-2-sulfamido-α-D-glucopyranosyl-(1→4)-1,6-anhydro-2-deoxy-2-sulfamido-β-D-glucopyranoside, disodium salt (PG2047)

A mixture of *2-deoxy-2-sulfamido-α-D-glucopyranosyl-(1→4)-1,6-anhydro-2-deoxy-2-sulfamido-3-O-benzyl-β-D-glucopyranoside, disodium salt* (12.9 mg, 20.8 μmol) and Pearlman's catalyst (5 mg) in purified water (2 mL) was subjected to 50 psi H_2 overnight. The mixture was filtered and lyophilised to yield 10.7 mg (98 %) of the title compound. ^1H NMR (400 MHz, D_2O) δ: 5.47 (br s, 1H, $H1^{I}$), 5.20 (d, 1H, J_{1-2} = 3.5, $H1^{II}$), 4.68 (br d, 1H, J_{5-4} = 5.5, H5), 4.07 (d, 1H, J_{gem} = 7.6, $H6A^{I}$), 3.98 (br s, 1H, $H3^{I}$), 3.75-3.64 (m, 4H), 3.52 (t, 1H, $J_{2-3-3-4}$ = 9.3, $H3^{II}$), 3.34 (t, 1H, $J_{3-4-4-5}$ = 9.3, $H4^{II}$), 3.13 (obs. dd[2], 1H, $H2^{II}$), 3.11 (br s, 1H, $H2^{I}$).

Example 3: PG2039 and PG2037

Step a: Methyl 3,4-di-O-acetyl-2,6-di-O-benzyl-α-D-galactopyranosyl-(1→4)-2,3,6-tri-O-benzyl-β-D-glucopyranoside

Methyl 2,3,6-tri-O-benzyl-β-D-glucopyranoside (287 mg; 618 μmol), 302 mg (618 μmol) of *ethyl 3,4-di-O-acetyl-2,6-O-dibenzyl-1-thio-β-D-galactopyranoside* [21] and 700 mg of 3Å molecular sieves were subjected to the general NIS glycosylation procedure using 181 mg (803 μmol, 1.3eq) of NIS. Flash chromatography (2.5 × 20 cm, gradient elution 1:5 to 1:3 EtOAc:Hexanes) yielded the title compound as a colourless gum (176 mg, 32%). ^1H NMR (400 MHz, $CDCl_3$, 400 MHz): 7.40-7.12 (m, 25H, Ph), 5.818 (d, 1H, $J_{1II-2II}$ = 3.6, $H1^{II}$), 5.481 (d, 1H, $J_{4II-3II}$ = 3.2, $H4^{II}$), 5.309 (dd, 1H, $J_{3II-2II}$ = 10.8, $J_{3II-4II}$ = 3.2, $H3^{II}$), 4.980 (d, 1H, J_{gem} = 11.6, a-$PhCH_2$), 4.904 (d, 1H, J_{gem} = 11.2, b-$PhCH_2$), 4.748 (d, 1H, J_{gem} = 11.6, a-$PhCH_2$), 4.67-4.57 (m, 3H, b-$PhCH_2$ and c-$PhCH_2$), 4.479 (d, 1H, J_{gem} = 12.8, d-$PhCH_2$), 4.443 (d, 1H, J_{gem} = 12.8, d-$PhCH_2$), 4.415 (d, 1H, J_{gem} = 11.6, e-$PhCH_2$), 4.360 (d, 1H, J_{1I-2I} = 8.0, $H1^{I}$), 4.201 (d, 1H, J_{gem} = 12.6, e-$PhCH_2$), 4.153 (t, 1H, $J_{5II-6axII}$ = 7.2, $J_{5II-6eqII}$ = 6.0, $H5^{II}$), 4.072 (t, 1H, J_{4I-3I} = 9.0, J_{4I-5I} = 9.0, $H4^{I}$), 3.858 (dd, 1H, $J_{2II-3II}$ = 10.8, $J_{2II-1II}$ = 3.6, $H2^{II}$), 3.82-3.76 (m, 3H, $H3^{I}$, $H6ax^{I}$ and $H6\ eq^{I}$), 3.597 (s, 3H, OMe), 3.62-3.57 (m, 1H, $H5^{I}$), 3.507 (t, 1H, J_{2I-3I} =

[1] Affected by the solvent suppression signal.
[2] Partially obscured by $H2^{I}$.

8.4, J_{2I-1I} = 8.0, H2^{I}), 3.347 (dd, 1H, $J_{6eqII-6axII}$ = 9.2, $J_{6eqII-5II}$ = 6.0, H6eq^{II}), 3.291 (dd, 1H, $J_{6axII-6eqII}$ = 9.2, $J_{6axII-5II}$ = 7.2, H6ax^{II}), 1.958 (s, 3H, OAc), 1.930 (s, 3H, OAc). ^{13}C NMR (100 MHz, $CDCl_3$, 100 MHz): 169.94 (CO), 169.78 (CO), 138.88, 138.35, 138.24, 137.73 and 137.64 (5x *ipso*-Ph), 128.25, 128.22, 128.21, 128.15, 128.12, 128.00, 127.80, 127.57, 127.52, 127.46, 127.41, 127.37, 126.93, 126.37, 104.40, 97.16, 84.63, 82.31, 74.42, 74.30, 73.70, 73.25, 73.16, 73.14, 72.98, 69.73, 69.07, 68.89, 67.64, 67.50, 56.86, 20.71, 20.55.

*Step b: Methyl 3,4-di-*O*-acetyl-*α*-*D*-galactopyranosyl-(1→4)-*β*-*D*-glucopyranoside.*

Following the standard debenzylation procedure, *methyl 3,4-di-*O*-acetyl-2,6-di-*O*-benzyl-*α*-*D*-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-*β*-*D*-glucopyranoside* (88 mg, 98.8 μmol) was deprotected to give the title compound as a colourless powder (42 mg, 97%). ^{1}H NMR (D_2O, 400 MHz): 5.394 (d, 1H, $J_{1II-2II}$ = 3.6, H1^{II}), 5.294 (d, 1H, $J_{4II-3II}$ = 3.2, H4^{II}), 4.953 (dd, 1H, $J_{3II-2II}$ = 10.4, $J_{3II-4II}$ = 3.2, H3^{II}), 4.229 (d, 1H, J_{1I-2I} = 8.4, H1^{I}), 4.080 (t, 1H, $J_{5II-6axII}$ = 6.4, $J_{5II-6eqII}$ = 6.0, H5^{II}), 3.965 (dd, 1H, $J_{2II-3II}$ = 10.4, $J_{2II-1II}$ = 3.6, H2^{II}), 3.803 (dd, 1H, $J_{6eqI-6eqI}$ = 12.0, $J_{6eqI-5I}$ = 1.6, H6eq^{I}), 3.67-3.59 (m, 2H, H6ax^{I} and H3^{I}), 3.54-3.40 (m, 4H, H4^{I}, H5^{I} and H6^{II}), 3.407 (s, 3H, OMe), 3.134 (dd, 1H, J_{2I-3I} = 9.2, J_{2I-1I} = 8.4, H2^{I}), 2.012 (s, 3H, OAc), 1.909 (s, 3H, OAc). ^{13}C NMR (D_2O, 100 MHz): 173.57, 173.47, 103.20, 99.71, 77.12, 76.30, 74.57, 73.09, 70.89, 69.94, 69.04, 66.45, 60.82, 60.18, 57.31, 20.34, 20.09.

*Step c: Methyl 2,6-di-*O*-sulfo-*α*-*D*-galactopyranosyl-(1→4)-2,3,6-tri-*O*-sulfo-*β*-*D*-glucopyranoside, pentasodium salt (PG2039)*

Following the standard sulfonation/deacetylation procedures, 42 mg (95.4 μmol) of *methyl 3,4-di-*O*-acetyl-*α*-*D*-galactopyranosyl-(1→4)-*β*-*D*-glucopyranoside* was converted to the title compound as a white powder (14.8 mg, 18%, CE: 6.12 min). ^{1}H NMR (D_2O, 400 MHz): 5.404 (d, 1H, $J_{1II-2II}$ = 3.6, H1^{II}), 4.756 (d, 1H, J_{1I-2I} = 3.6, H1^{I}), 4.60 (overlappped with water, 1H, H3^{I}), 4.448 (dd, 1H, J_{2I-3I} = 3.2, H2^{I}), 4.296 (dd, 1H, $J_{2II-3II}$ = 10.0, H2^{II}), 4.23-4.00 (m, 7H, H6^{I}, H5^{I}, H6^{II}, H4^{I} and H5^{II}), 3.958 (dd, 1H, $J_{3II-4II}$ = 3.6, $J_{4II-5II}$ = 0.8, H4^{II}), 3.930 (dd, 1H, H3^{II}), 3.367 (s, 3H, CH_3O).

*Step d: Methyl 2,6-di-*O*-benzyl-3,4-di-*O*-methyl-*α*-*D*-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-*β*-*D*-glucopyranoside*

Following the standard deacetylation and methylation procedures, *methyl 3,4-di-*O*-acetyl-2,6-di-*O*-benzyl-*α*-*D*-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-*β*-*D*-glucopyranoside* (72 mg, 80.8 μmol) was converted into the title compound as colourless gum (62.7 mg, 93%). ^{1}H NMR ($CDCl_3$, 400 MHz): 7.35-7.08 (m, 25H, Ph), 5.717 (d, 1H, $J_{1II-2II}$ = 3.6, H1^{II}), 4.856 (d, 1H, J_{gem} = 11.2, a-$PhCH_2$), 4.843 (d, 1H, J_{gem} = 10.8, b-$PhCH_2$), 4.695 (d, 2H, J_{gem} = 12.0,

a-$PhCH_2$ and c-$PhCH_2$), 4.631 (d, 1H, J_{gem} = 12.4, d-$PhCH_2$), 4.571 (d, 1H, J_{gem} = 10.8, b-$PhCH_2$), 4.500 (d, 1H, J_{gem} = 12.4, d-$PhCH_2$), 4.450 (d, 1H, J_{gem} = 11.6, c-$PhCH_2$), 4.433 (d, 1H, J_{gem} = 11.2, e-$PhCH_2$), 4.359 (d, 1H, J_{gem} = 11.2, e-$PhCH_2$), 4.303 (d, 1H, J_{1I-2I} = 7.6, $H1^I$), 3.949 (t, 1H, J_{4I-3I} = 9.0, J_{4I-5I} = 9.0, $H4^I$), 3.871 (dd, 1H, $J_{5II-6axII}$ = 7.2, $J_{5II-6eqII}$ = 6.4, $H5^{II}$), 3.791 (dd, 1H, $J_{2II-3II}$ = 10.4, $J_{2II-1II}$ = 3.6, $H2^{II}$), 3.77-3.68 (m, 4H, $H4^{II}$, $H3^I$, H6ax^I and H6eq^I)), 3.59-3.53 (m, 2H, $H5^I$ and $H6^{II}$), 3.551 (s, 3H, OMe), 3.51-3.40 (m, 3H, $H3^{II}$, $H6^{II}$ and $H2^I$), 3.492 (s, 3H, OMe), 3.433 (s, 3H, OMe).

*Step e: Methyl 3,4-di-*O*-methyl-α-*D*-galactopyranosyl-(1→4)-β-*D*-glucopyranoside*

Following the standard debenzylation procedure, *methyl 2,6-di-*O*-benzyl-3,4-di-*O*-methyl-α-*D*-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-*D*-glucopyranoside* (62.7 mg, 75.1 μmol) was deprotected to give the title compound as colourless gum (28 mg, 97%). ^{1}H NMR (D_2O, 400 MHz): 5.232 (d, 1H, $J_{1II-2II}$ = 4.4, $H1^{II}$), 4.217 (d, 1H, J_{1I-2I} = 8.0, $H1^I$), 3.83-3.75 (m, 3H, $H4^{II}$, $H5^{II}$ and $H6^I$), 3.682 (dd, 1H, $J_{2II-3II}$ = 10.4, $J_{2II-1II}$ = 4.4, $H2^{II}$), 3.64-3.52 (m, 4H, $H6^I$, $H3^{II}$ and $H6^{II}$), 3.47-3.38 (m, 3H, $H4^I$, $H5^I$ and $H3^{II}$), 3.400 (s, 3H, OMe), 3.340 (s, 6H, 2xOMe), 3.117 (dd, 1H, J_{2I-3I} = 9.6, J_{2I-1I} = 8.0, $H2^I$). ^{13}C NMR (D_2O, 100 MHz): 103.20, 99.64, 79.35, 76.92, 76.34, 75.35, 74.65, 73.06, 72.03, 68.00, 61.02, 60.89, 60.86, 57.30, 56.94.

*Step f: Methyl 3,4-di-*O*-methyl-2,6-di-*O*-sulfo-α-*D*-galactopyranosyl-(1→4)-2,3,6-tri-*O*-sulfo-β-*D*-glucopyranoside, pentasodium salt (PG2037)*

Following the standard sulfonation procedure, *methyl 3,4-di-*O*-methyl-α-*D*-galactopyranosyl-(1→4)-β-*D*-glucopyranoside* (28 mg, 72.8 μmol) gave the title compound (3.2 mg, 4.9%). ^{1}H NMR (400 MHz, D_2O): 5.357 (d, 1H, $J_{1II-2II}$ = 3.2, $H1^{II}$), 4.766 (d, 1H, J_{1I-2I} = 3.6, $H1^I$), 4.60 (overlappped with water, 1H, $H3^I$), 4.455 (dd, 1H, J_{2I-3I} = 2.8, $H2^I$), 4.304 (dd, 1H, $J_{2II-3II}$ = 10.0, $H2^{II}$), 4.22-3.99 (m, 5H, $H5^I$, $H6^I$, $H4^I$ and $H5^{II}$), 4.002 (d, 2H, $J_{5II-6II}$ = 6.8, $H6^{II}$), 3.886 (d, 1H, $J_{3II-4II}$ = 3.2, $H4^{II}$), 3.667 (dd, 1H, $H3^{II}$), 3.398 (s, 3H, CH_3O), 3.367 (s, 3H, CH_3O), 3.356 (s, 3H, CH_3O).

Example 4: PG2053 and PG2042

*Methyl 4-*O*-Allyl-2,3-di-*O*-sulfo-α-*L*-rhamnoside, disodium salt (PG2053).*

The title compound was obtained from *methyl 2,3-*O*-isopropylidene-α-*L*-rhamnopyranoside* [22] *via* the general alkylation (with allyl bromide) and deprotection procedure followed by the general sulfonation procedure, as a colourless powder. CE t_m = 10.48 min. ^{1}H NMR (400 MHz, D_2O) δ 1.19 (d, 3 H, $J_{5,6}$ 6.4 Hz; H-6), 3.26 (s, 3 H; OMe); 3.29-3.40 (m, 1 H; H-4), 3.59-3.67 (m, 1 H; H-5), 4.00-4.05, 4.18-4.22 (2 m, 2 H; OCH_2),

4.41-4.42 (m, 1 H; H-3), 4.63-4.64 (m, 2 H; H-2), 4.83 (s, 1 H; H-1), 5.07-5.21 (m, 2 H; $=CH_2$), 5.76-5.88 (m, 1 H; =CH).

When a reduced quantity (1 eq.) of SO_3•trimethylamine was employed, *methyl 4-O-allyl-2-O-sulfo-α-L-rhamnoside, sodium salt (PG2042)* was exclusively obtained. CE t_m > 25.00 min. ^{1}H NMR (400 MHz, D_2O) δ 1.19 (d, 3 H, $J_{5,6}$ 6.4 Hz; H-6), 3.16 (t, 1 H, $J_{3,4}$ 3.1, $J_{4,5}$ 9.7 Hz; H-4), 3.25 (s, 3 H; OMe), 3.54-3.58 (m, 1 H; H-5), 3.76 (dd, 1 H, $J_{2,3}$ 9.7 Hz; H-3), 4.03-4.18 (m, 2 H; OCH_2), 4.34-4.35 (m, 1 H; H-2), 4.80 (s, 1 H; H-1), 5.08-5.22 (m, 2 H; $=CH_2$), 5.78-5.88 (m, 1 H; =CH).

Example 5: PG2024

Methyl 4-O-Benzyl-2,3-di-O-sulfo-α-L-rhamnoside, disodium salt (PG2024)

The title compound was obtained from *methyl 2,3-O-isopropylidene-α-L-rhamnopyranoside via* the general alkylation (with benzyl bromide) and deprotection procedure followed by the general sulfonation procedure, as a colourless powder. CE t_m = 10.82 min. ^{1}H NMR (400 MHz, D_2O) δ 1.00 (d, 3 H, $J_{5,6}$ 6.8 Hz; H-6), 3.23 (s, 3 H; OMe); 3.78-3.80 (m, 1 H; H-4), 3.88-3.94 (m, 1 H; H-5), 4.41-4.43 (m, 1 H; H-2), 4.52-4.56 (m, 2 H; H-3), 4.54, 4.78 (AB quartet, $J_{A,B}$ 12.0 Hz; CH_2Ph), 4.90 (dd, 1 H, $J_{1,2}$ 1.2 Hz; H-1), 7.20-7.36 (m, 5 H; ArH).

Example 6: PG2054

Step a: Methyl 4-O-benzoyl-α-L-rhamnoside

A solution of *methyl 2,3-O-isopropylidene-α-L-rhamnopyranoside* (200 mg, 920 μmol), benzoyl chloride (193 mg, 1.38 mmol) and Et_3N (364 μL, 2.76 mmol) in DCM (10 mL) was stirred overnight. The resulting suspension (Et_3N•HCl precipitates) was diluted with DCM (50 mL) and washed with $NaHCO_3$ (sat. aqueous), water then brine, dried ($MgSO_4$) and evaporated. The residue was taken up in 50 mL of 1:1 MeCN:H_2O and p-TsOH (10 mg) was added. The resulting solution was stirred until the reaction was complete (TLC, ~4 h), evaporated and subjected to flash chromatography (1:1 EtOAc:hexanes) to give 165 mg (64 % over two steps) of the title compound as a colourless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03-8.00 (m, 2H, Hortho), 7.55 (tt, 1H, $J_{Hp\text{-}Hm}$ = 7.5, $J_{Hp\text{-}Ho}$ = 1.3, Hpara), 7.43-7.39 (m, 2H, Hmeta), 5.09 (dis t, 1H, $J_{4\text{-}3\text{-}4\text{-}5}$ = 9.3, H4), 4.73 (br s, 1H, H1), 4.01-3.97 (m, 2H, H2+H3), 3.91 (dq, 1H, $J_{4\text{-}5}$ = 9.7, $J_{5\text{-}6}$ = 6.4, H5), 3.53-3.46 (br s, 2H, OH), 3.38 (s, 3H, OMe), 1.25 (d, 3H, H6). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.1, 133.3, 129.8, 129.5, 128.3, 100.6, 75.7, 70.8, 70.1, 65.7, 55.0, 17.4.

Step b: Methyl 4-O-Benzoyl-2,3-di-O-sulfo-α-L-rhamnoside, Disodium salt (PG2054)

The title compound was obtained from *methyl 4-O-benzoyl-α-L-rhamnoside via* the general sulfonation procedure as a colourless powder. CE t_m = 11.14 min. ^{1}H NMR (400 MHz, D_2O) δ 1.14 (d, 3 H, $J_{5,6}$ 6.3 Hz; H-6), 3.33 (s, 3 H; OMe), 3.99-4.07 (m, 1 H; H-5), 4.66-4.73 (m, 2 H; H-2, -3), 4.95 (d, 1 H, $J_{1,2}$ 1.4 Hz; H-1), 5.04 (t, 1 H, $J_{3,4=4,5}$ 9.6 Hz; H-4), 7.35-7.41, 7.53-7.55, 7.92-7.93 (3 m, 5 H; Ph).

Example 7: PG2041

Step a: 4,6-O-Benzylidene-1,2-dihydro-D-glucal.

A mixture of *tri-O-acetyl-D-glucal* (1.7 g, 6.25 mmol), AcOH (50 μL) and $Pd(OH)_2/C$ (100 mg) in MeOH (15 mL) was vigorously stirred under H_2 (1 atm.) overnight. The mixture was filtered, the solvent evaporated and the residue subjected to flash chromatography (10-50% EtOAc/hexanes) to yield *tri-O-acetyl-1,2-dihydro-D-glucal* as a colourless oil. This residue was co-evaporated (2 × 10 mL MeCN) then subjected to the Zemplén deacetylation general procedure to yield *1,2-dihydro-D-glucal* as a colourless oil (825 mg, 89%). This residue was co-evaporated (2 × 10 mL MeCN).

p-TsOH.H_2O (50 mg) was added to a solution of the *1,2-dihydro-D-glucal* (495 mg, 3.34 mmol) and α,α-dimethoxytoluene (753 μL, 5.01 mmol) in DMF (5 mL) and the combined mixture stirred (60°, 1 h). Et_3N (100 μL) was introduced and the solvent was evaporated. The residue was subjected to flash chromatography (0-5% MeOH/$CHCl_3$) to yield the title compound as colourless needles (503 mg, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.72-2.01 (m, 2 H; H-2), 3.27-3.33 (m, 1 H; H-5), 3.41 (dd, 1 H, $J_{3,4}$ 8.8, $J_{5,6}$ 9.1 Hz; H-4), 3.49-3.56 (m, 1 H; H-3), 3.67 (t, 1 H, $J_{5,6=6,6}$ 10.3 Hz; H-6), 3.81-3.87, 3.93-3.98 (2 m, 2 H; H-1), 4.25 (dd, 1 H; $J_{5,6}$ 4.9 Hz; H-6), 5.53 (s, 1 H; C*H*Ph), 7.23-7.52 (m, 5 H, CHPh). ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.47 (C-2); 66.46, 69.07, 69.64, 71.32 (4 C; C-1,-4,-5,-6), 84.14, (C-3), 102.16 (*C*HPh), 126.43, 128.55, 129.34, 137.50 (4 C; Ph).

Step b: 3-O-Benzyl-4,6-di-O-sulfo-1,2-dihydro-D-glucal, Disodium salt (PG2041).

4,6-O-Benzylidene-1,2-dihydro-D-glucal was subjected to the alkylation (benzyl bromide), de-protection and sulfonation general procedures to yield the title compound as a colourless powder. CE t_m = 15.40 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48-1.53, 1.97-2.03 (2 m, 2 H; H-2), 3.30-3.71 (m, 1 H; H-1), 3.52-3.57 (m, 1 H; H-5), 3.60-3.66 (m, 1 H; H-3), 3.78-3.83 (m, 1 H; H-1), 3.97 (dd, 1 H, $J_{5,6}$ 8.0, $J_{6,6}$ 11.4 Hz; H-6), 3.98 (t, 1 H, $J_{3,4=4,5}$ 8.9 Hz; H-4), 4.34 (dd, 1 H, $J_{5,6}$ 2.3 Hz; H-6), 4.52-4.67 (m, 2 H; CH_2Ph), 7.21-7.36 (m, 5 H; Ph).

Example 8: PG2030

Step a: 1,6-Anhydro-3-O-methyl-β-D-glucopyranose.

p-Toluenesulfonyl chloride (790 mg, 4.14 mmol) was added to a cooled (0°) suspension of *3-O-methyl-D-glucopyranose* (804 mg, 4.14 mmol) in pyridine (10 mL) and the reaction mixture stirred (0°→r.t, 1.5 h). Ac_2O (1.5 mL, 15 mmol) and *N,N*-dimethylaminopyrdine (50 mg) were then introduced and stirring continued (r.t., 4 h). The mixture was then cooled (0°) and MeOH (3 mL) was added and stirring maintained (10 min) prior to evaporation of the solvent. The residual oil was dissolved (EtOAc) and subjected to workup yielding the tosylate as a pale yellow coloured oil (1.93 g). A mixture of the crude tosylate (1.93 g) and NaOH (20 mL of 1.0 M, 20 mmol) in EtOH (20 mL) was heated (80°, 1 h). The mixture was neutralised with acetic acid and the solvent evaporated and co-evaporated (toluene). The crude residue was treated with pyridine (10 mL), Ac_2O (5 mL) and *N,N*-dimethylaminopyridine (50 mg) and the combined mixture stirred (r.t., o/n). The mixture was treated with ice-water (10 mL) and stirring continued (r.t., 3 h) before being subjected to workup (EtOAc). The residual oil was subjected to flash chromatography (20-50% EtOAc/hexanes) to yield an inseparable mixture of *2,4-di-O-acetyl-1,6-anhydro-3-O-methyl-β-D-glucopyranose* (**a**) and *1,2,4-tri-O-acetyl-3-O-methyl-6-O-tosyl-α-D-glucopyranose* (**b**) (in a ratio of 3:1) as a pale yellow oil (466 mg). The ratio was determined by integration of the H-1 and 3-OMe signals observed in the ^{1}H NMR spectrum. Partial ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.32 (s, 3 H; OMe **b**), 3.45 (s, 3 H; OMe **a**); 5.22 (br s, 1 H; H-1 **b**), 5.42 (br s, 1 H; H-1 **a**). The mixture of the two compounds (456 mg) was subjected to the Zemplén deacetylation general method and the residue subjected to flash chromatography (0-5% MeOH/EtOAc) to yield the title compound as a colourless oil (162 mg, 33%, 3 steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.27-3.30 (m, 1 H; H-3), 3.38 (s, 3 H; OMe), 3.57-3.59 (m, 1 H; H-2), 3.63-3.65 (m, 1 H; H-4), 3.70 (dd, 1 H, $J_{5,6}$ = 5.6, $J_{6,6}$ = 7.2 Hz; H-6), 4.06 (d, 1 H, $J_{6,6}$ = 7.2 Hz; H-6), 4.48-4.51 (m, 1 H; H-5), 4.39 (br s, 1 H; H-1).

Step b: 1,6-Anhydro-4-O-benzyl-3-O-methyl-β-D-glucopyranose.

A mixture of *1,6-anhydro-3-O-methyl-β-D-glucopyranose* (155 mg, 0.88 mmol) and Bu_2SnO (241 mg, 0.97 mmol) in toluene (18 mL) was heated under reflux (with azeotropic removal of water) until the solution was one-half the original volume. The mixture was cooled (80°), BnBr (104 μL, 0.88 mmol) and Bu_4NBr (567 mg, 1.76 mmol) were introduced and stirring continued (o/n). The mixture was treated with MeOH (2 mL) and H_2O (1 mL) with continued stirring (10 min) prior to evaporation of the solvent. The residue was subjected to

workup (EtOAc) and flash chromatography (20-60% EtOAc/ hexanes) to yield two compounds.

Firstly, the title compound was produced as a colourless oil (94 mg, 40%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.58 (d, 1 H, $J_{2,OH}$ 6.4 Hz; OH), 3.32-3.43 (m, 5 H; H-3, H-4, OMe), 3.52-3.57 (m, 1 H; H-2), 3.68-3.72, 4.01-4.04 (2 m, 2 H; H-6), 4.55-4.58 (m, 1 H; H-5), 4.64 (s, 2 H; CH_2Ph), 5.39-5.40 (m, 1 H; H-1), 7.28-7.36 (m, 5 H; ArH).

Secondly, *1,6-anhydro-2-*O*-benzyl-3-*O*-methyl-*β-D*-glucopyranose* was afforded as a colourless oil (91 mg, 39%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.90 (br s, 1 H; OH), 3.31-3.34 (m, 4 H; H-2, OMe), 3.36-3.38 (m, 1 H; H-3), 3.58 (br s, 1 H; H-4), 3.68 (dd, 1 H, $J_{5,6}$ 6.0 Hz, $J_{6,6}$ 7.2 Hz; H-6), 4.08 (dd, 1 H, $J_{5,6}$ 0.8 Hz, $J_{6,6}$ 7.2 Hz; H-6), 4.47-4.49 (m, 1 H; H-5), 4.56, 4.62 (AB quartet, $J_{A,B}$ 12.0 Hz; CH_2Ph), 5.40-5.41 (m, 1 H; H-1), 7.26-7.36 (m, 5 H; ArH).

*Step c: 1,6-Anhydro-4-*O*-benzyl-3-*O*-methyl-2-*O*-sulfo-β-D-glucopyranose, sodium salt (PG2030)*

*1,6-Anhydro-4-*O*-benzyl-3-*O*-methyl-β-D-glucopyranose* (84 mg, 0.32 mmol) was sulfonated according to the general procedure and subjected to flash chromatography (50/2/1→10/2/1 EtOAc/MeOH/H_2O) prior to SEC to yield the title compound as a pale yellow coloured powder (70 mg, 60%); CE t_m = 5.62 min; ^{1}H NMR (400 MHz, D_2O) δ 3.19 (s, 3 H; OCH_3); 3.43-3.45 (m, 1 H; H-4), 3.52-3.53 (m, 1 H; H-3), 3.57 (dd, 1 H, $J_{5,6}$ = 5.9 Hz, $J_{6,6}$ = 7.8 Hz; H-6), 3.82 (dd, 1 H, $J_{5,6}$ = 1.1 Hz, $J_{6,6}$ = 7.8 Hz; H-6), 3.97-3.99 (m, 1 H; H-5), 4.59-4.61 (m, 3 H; H-2, CH_2Ph), 5.41 (br s, 1 H; H-1), 7.22-7.34 (m, 5 H; ArH).

Example 9: PG2012 and PG2013

Step a: N*-benzyl-*N*-(cyclohexylacetamido)-1,2,3,4-tetra-O-acetyl-*D*-glucuronamide*

Following the general procedure for the Ugi reaction, D-glucuronic acid (0.950 g, 4.89 mmol), and solutions of each of the following three reagents: benzylamine (2 M in MeOH, 2.45 mL, 4.89 mmol), formaldehyde (2 M in MeOH, 2.45 mL, 4.89 mmol) and cyclohexylisocyanide (1 M in MeOH, 4.89 mL, 4.89 mmol) were loaded into a reaction vessel and the mixture stirred at r.t. for 19 h. The volatiles were removed under reduced pressure and dried under high vacuum to afford N*-benzyl-*N*-(cyclohexylacetamido)-*D*-glucuronamide* as a yellow foam.

Following the general procedure for acetylation, the above crude Ugi product was peracetylated to give the title compound as pale-yellow foam 1.929 g, 66% (two steps, Rf = 0.37, hexane-EtOAc 1:1) after flash chromatography (gradient elution with hexanes-EtOAc 2:1 to 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz) was very complicated due to the presence of anomers and

rotamers. The spectrum was not simplified after the temperature was raised to 55 °C. However, in pyridine-d_6 at 100 °C, each set of rotamers was coalesced in some degree into much more simplified structure, thus two anomers were clearly observed (α:β ratio = 69:31). ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): 7.41-7.14 (m, 5H, Ph), 6.337 (d, 0.39H, J= 3.6), 6.300 (d, 0.29H, J= 3.6), 5.969 (br d, 0.52H, J= 8), 5.823 (br d, 0.09H, J= 8.4), 5.66-5.41 (m, 2.25H), 5.28-5.09 (m, 1.3H), 4.92-4.58 (m, 2.25H), 4.411 (d, J= 10) and 4.395 (d, J= 14, 0.55H), 4.271 (d, 0.11H, J= 9.6), 4.219 (d, 0.09H, J= 17.2), 4.125 (d, 0.17H, J= 14), 4.098 (d, 0.17H, J= 14.4), 3.994 (d, J= 15.2) and 3.963 (d, J= 14.8, 0.89H), 3.82-3.59 (m, 2.04H), 2.190, 2.111, 2.038, 2.033, 2.025, 2.023, 2.016, 2.014, 2.008, 1.998, 1.983, 1.944 and 1.927 (all singlet, 12H, Ac), 1.89-1.55 (m, 5H, cyclohexyl-CH_2), 1.41-0.83 (m, 5H, cyclohexyl-CH_2). ^{1}H NMR ($CDCl_3$, 400 MHz, 55 °C): 7.38-7.16 (m, 5H, Ph), 6.336 (d, J= 3.2,) and 6.153 (d, J= 3.2, 0.7H), 5.939 (br d, 0.6H, J= 6.8), 5.721 (br d, 0.2H, J= 7.2), 5.65-5.55 (m, 1.3H), 5.52-5.41 (m, 1H,), 5.28-5.10 (m, 1.4H), 4.85-4.58 (m, 2.4H), 4.48-4.40 (m, 0.6H), 4.318 (d, 0.1H, J= 9.2), 4.205 (d, 0.1H, J= 17.6), 4.02-3.93 (m, 0.9H), 3.84-3.62 (m, 2.2H), 2.179, 2.090, 2.021, 2.012, 2.001, 1.989, 1.983, 1.975, 1.968, 1.959 and 1.935 (all singlet, 12H, Ac), 1.88-1.56 (m, 5H, cyclohexyl-CH_2), 1.42-0.88 (m, 5H, cyclohexyl-CH_2). ^{1}H NMR (pyridine-d_6, 400 MHz, δ7.22, 100 °C): only typical sugar protons are given; the remaining signals (except acetate singlets) were complicated and appeared as broad lumps. α-anomer, 6.672 (d, J = 3.6, glu-H1), 5.456 (dd, J= 9.6, 3.6, glu-H2); β-anomer, 6.206 (d, J= 8.0, glu-H1), 5.741 (t, J= 9.2, glu-H4 or H5), 5.515 (dd, J= 8.8, 8.0, glu-H2).

Step b: N-*benzyl*-N-*(cyclohexylacetamido)-1,2,3,4-tetra*-O-*sulfo*-α-D-*glucuronamide, tetrasodium salt (PG2012) and* N-*benzyl*-N-*(cyclohexylacetamido)-1,2,3-tri*-O-*sulfo*-α-D-*glucuronamide, trisodium salt (PG2013)*

Following the general procedure for deacetylation, the above tetraacete (0.441 g, 0.747 mmol) was deacetylated to give N-*benzyl*-N-*(cyclohexylacetamido)*-D-*glucuronamide* as pale-yellow glass (0.316 g, 100%).

Following the general procedure for sulfonation, the above tetrol (0.257 g, 0.608 mmol) was sulfonated (using sulfur trioxide pyridine complex, 60 °C, 19 h). The residue was co-evaporated with toluene and purified by flash chromatography [2.5 × 20cm, eluted with EtOAc, MeCN, MeCN-Et_3N (10:1), MeCN-Et_3N-H_2O (110:2:11)]. The fractions were divided into two parts according to TLC and CE. The less polar part was purified again by flash chromatography, LH20 (×2) and ion exchange chromatography to give trisulfate PG2013 as white fluffy powder after lyophilisation (19.3 mg, 4.4%). ^{1}H NMR (D_2O, 400 MHz): two

rotamers in a ratio of 56:44. major rotamer, δ 7.36-7.11 (m, 5H, Ph), 5.946 (d, 1H, J= 3.2, H1), 4.894 (d, 1H, J= 9.6, H5), 4.748 (d, 1H, J= 16, a-CH_2), 4.685 (d, 1H, J= 16, a-CH_2), 4.502 (t, 1H, J= 10.4, 9.6, H3), 4.306 (dd, 1H, J= 9.6, 3.6, H2), 4.005 (t, 1H, J= 9.6, 8.8, H4), 3.869 (s, 2H, b-CH_2), 3.42-3.32 (m, 1H, cyclohexyl-CHN), 1.64-1.36 (m, 5H, cyclohexyl-CH_2), 1.20-0.92 (m, 5H, cyclohexyl-CH_2); minor rotamer, 7.36-7.11 (m, 5H, Ph), 5.905 (d, 1H, J= 3.2, H1), 4.578 (d, 1H, J= 10, H5), 4.523 (s, 2H, c-CH_2), 4.478 (t, 1H, J= 10.4, 9.6, H3), 4.321 (d, 1H, J= 17.6, d-CH_2), 4.281 (dd, 1H, J= 9.6, 3.2, H2), 4.039 (t, 1H, J= 9.6, 9.2, H4), 3.900 (d, 1H, J = 17.6, d-CH_2), 3.42-3.32 (m, 1H, cyclohexyl-CHN), 1.64-1.36 (m, 5H, cyclohexyl-CH_2), 1.20-0.92 (m, 5H, cyclohexyl-CH_2). ^{13}C NMR (D_2O, 100 MHz, no reference): double-up of each signals due to two rotamers, 169.96 (amide-CON), 169.75 (amide-CON), 168.91 (amide-CON), 168.85 (amide-CON), 135.45 (*ipso*-Ph), 135.20 (*ipso*-Ph), 129.16, 129.07, 128.47, 128.32, 128.20 and 128.13 (*meta-*, *ortho-* and *para*-Ph), 95.67 and 95.65 (glu-C1), 77.84 and 77.75 (glu-C3), 73.76 and 73.71 (glu-C2), 70.66 and 70.18 (glu-C4), 69.23 and 68.70 (glu-C5), 52.87 (a-CH_2), 51.12 (c-CH_2), 50.32 (d-CH_2), 50.02 (b-CH_2), 49.25 and 49.00 (cyclohexyl-CHN), 31.89 and 31.86, 25.08 and 25.05, 24.47 and 24.38 (cyclohexyl-CH_2). ES-LRMS (+ve, *m/z*): $C_{21}H_{27}N_2Na_3O_{16}S_3$ required 728.02, found 751 ($M+Na^+$), 729 ($M+H^+$); ES-HRMS (+ve, *m/z*): $M+Na^+$, $C_{21}H_{27}N_2Na_4O_{16}S_3$ required 751.0113, found 750.1087; $M+H^+$, $C_{21}H_{28}N_2Na_3O_{16}S_3$ required 729.0294, found 729.0242.

The polar part was purified by LH20 column (×2) and ion exchange column to give tetrasulfate PG2012 as an off-white powder after lyophilisation (7.6 mg, 1.5%). ^1H NMR (D_2O, 400 MHz): two rotamers in a molar ratio of 70:30. Major rotamer, δ 7.34-7.16 (m, 5H, Ph), 5.954 (d, 1H, J= 3.6, H1), 5.235 (d, 1H, J= 9.6, H5), 4.904 (d, 1H, J= 15.6, a-CH_2), 4.67-4.57 (overlapped with water, 1H, H3), 4.536 (t, 1H, J= 9.6, 8.8, H4), 4.466 (d, 1H, J= 15.6, a-CH_2), 4.394 (dd, 1H, J= 9.8, 3.4, H2), 3.927 (d, 1H, J= 16.8, b-CH_2), 3.749 (d, 1H, J= 16.8, b-CH_2), 3.30-3.20 (m, 1H, cyclohexyl-CHN), 1.65-1.35 (m, 5H, cyclohexyl-CH_2), 1.18-0.92 (m, 5H, cyclohexyl-CH_2); minor rotamer, 7.34-7.16 (m, 5H, Ph), 5.912 (d, 1H, J= 3.4, H1), 4.77-4.72 (m, 2H, H5 and H3 or H4), 4.689 (d, 1H, J = 15.2, c-CH_2), 4.67-4.56 (overlapped with water, 1H, H4 or H3), 4.373 (dd, 1H, J= 9.8, 3.4, H2), 4.256 (d, 1H, J= 18.4, d-CH_2), 4.215 (d, 1H, J= 15.2, c-CH_2), 3.936 (d, 1H, J= 18.4, d-CH_2), 3.36-3.26 (m, 1H, cyclohexyl-CHN), 1.65-1.35 (m, 5H, cyclohexyl-CH_2), 1.18-0.92 (m, 5H, cyclohexyl-CH_2). ^{13}C NMR (D_2O, 100 MHz, no reference): major rotamer, 172.35 (amide-CON), 171.69 (amide-CON), 137.22 (*ipso*-Ph), 131.71 and 131.58 (*meta-* and *ortho*-Ph), 131.11 (*para*-Ph), 97.68 (glu-C1), 78.08 (glu-C4), 77.60 (glu-C3), 76.43 (glu-C2), 70.10 (glu-C5), 55.81 (a-CH_2), 53.17

(b-CH_2), 51.77 (cyclohexyl-CHN), 34.17 (cylcohexyl-CH_2), 27.56 (cylcohexyl-CH_2), 27.13 (cylcohexyl-CH_2); minor rotamer (only typical peaks shown), 97.65 (glu-C1), 78.22 (glu-C4), 77.77 (glu-C3), 76.33 (glu-C2), 71.01 (glu-C5), 53.26 (d-CH_2), 53.79 (c-CH_2), 52.10 (cyclohexyl-CHN), 34.28 (cylcohexyl-CH_2), 27.52 (cylcohexyl-CH_2), 27.08 (cylcohexyl-CH_2). ES-MS (+ve, *m/z*): $C_{21}H_{26}N_2Na_4O_{19}S_4$ required 829.96, found 853 ($M+Na^+$), 831 ($M+H^+$). ES-HRMS (+ve, *m/z*): $M+Na^+$, $C_{21}H_{26}N_2Na_5O_{19}S_4$ required 852.9501, found 852.9334; $M+H^+$, $C_{21}H_{27}N_2Na_4O_{19}S_4$ required 830.9682, found 830.9635.

Example 10: PG2064

*Step a: 2-(*N*-acetyl-*N*-cyclohexyl)amino-*N*-(methyl 2,3,4-tri-*O*-benzyl-6-deoxy-*α*-D-mannopyranos-6-yl)acetamide*

Following the general procedure for the Ugi reaction, a solution of each of the following four reagents: acetic acid (2 M in MeOH, 60 μL, 119 μmol), cyclohexylamine (2 M in MeOH, 60 μL, 119 μmol), formaldehyde (2 M in MeOH, 60 μL, 119 μmol) and *methyl 2,3,4-tri-*O*-benzyl-6-deoxy-6-isocyano-*α*-*D*-mannopyranoside* (0.721 M in $CHCl_3$, 150 μL, 108 μmol) was loaded into a 4 mL sample vial and the mixture stirred at 60 °C for 19 h. The volatiles were removed under reduced pressure and purified by flash chromatography (gradient elution with hexane-EtOAc 4:1 to 1:4) to afford the title compound as a colourless gum, 42 mg, 60% (Rf = 0.49, EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz): two rotamers in a ratio of 72:28. δ 7.38-7.26 (m, 15H, 3 × C_6H_5), 6.933 (t, 72% × 1H, J = 4.4, NH in major rotamer), 6.357 (t, 28% × 1H, J = 5.8, NH in minor rotamer), 4.91-4.41 (m, 7H, sugar-H1 and 3 × $PhCH_2$), 4.04-3.42 (m, 9H, sugar-H2-6, NCH_2CO and cyclohexyl-CH), 3.305 (s, 72% × 3H, CH_3O in major rotamer), 3.266 (s, 28% × 3H, CH_3O in minor rotamer), 2.067 (s, 72% × 3H, CH_3CO in major rotamer), 2.012 (s, 28% × 3H, CH_3CO in major rotamer), 1.85-1.00 (m, 10H, cyclohexyl-CH_2).

*Step b: 2-(*N*-acetyl-*N*-cyclohexyl)amino-*N*-(methyl 6-deoxy -2,3,4-tri-*O*-sulfo-*α*-D-mannopyranos-6-yl)acetamide, trisodium salt (PG2064)*

Following the general procedure for deprotection of benzyl ethers, a mixture of the above tribenzyl ether (42 mg, 0.065 mmol), 20% palladium on activated charcoal (22 mg) in MeOH (2 mL) was stirred under hydrogen atmosphere at 50 psi for 10 h. General work-up gave the triol intermediate as a colourless gum. Following the general procedure for sulfonation, the triol was sulfonated (sulfur trioxide trimethylamine complex, 60 °C, 19 h) and the crude was evaporated. The residue was purified via sequential SEC (Bio Gel P-2 followed by LH20). The pure product was converted to the sodium salt by passing through an ion

exchange column to give the title compound as a white fluffy powder after lyophilisation (3.1 mg, 7.0%, two steps). ^{1}H NMR (D_2O, int. ref. acetone at 2.05, 400 MHz): two rotamers in a ratio of 63:37. δ 4.844 (s, 1H, sugar-H1), 4.678 (s, 1H, sugar-H2), 4.51-4.45 (m, 1H, sugar-H3), 4.240 (t, 37% × 1H, J = 9.6, sugar-H4 in minor rotamer), 4.214 (t, 63% × 1H, J = 9.6, sugar-H4 in major rotamer), 3.980 (s, 37% × 2H, $COCH_2N$ in minor rotamer), 3.825 (s, 63% × 2H, $COCH_2N$ in major rotamer), 3.78-3.59 (m, 3H, sugar-H5, one sugar-H6 and cyclohexyl-CH), 3.31-3.17 (m, 4H, one sugar-H6 and CH_3O [3.253, s, 3H]), 2.060 (s, 67% × 3H, CH_3CO in major rotamer), 1.900 (s, 33% × 3H, CH_3CO in minor rotamer), 1.70-0.88 (m, 10H, cyclohexyl-CH_2).

Example 11: PG2068

Step a

Following the general procedure for the Ugi reaction, monomethyl succinate (15.7 mg, 0.119 mmol) and a solution of each of the following three reagents: ethylamine (2 M in MeOH, 60 μL, 119 μmol), formaldehyde (2 M in MeOH, 60 μL, 119 μmol) and *methyl 2,3,4-tri-O-benzyl-6-deoxy-6-isocyano-α-D-mannopyranoside* (0.721 M in $CHCl_3$, 150 μL, 108 μmol) was loaded into a 2 mL sample vial and the mixture stirred at r.t. for 19 h. The volatiles were removed under reduced pressure and purified by flash chromatography (gradient elution with hexane-EtOAc 1:1 to 1:4 then EtOAc) to afford pure product as a colourless gum (46.8 mg, 65%). ^{1}H NMR ($CDCl_3$, 400 MHz): two rotamers in a ratio of 73:27. δ 7.38-7.25 (m, 15H, Ph), 6.598 (t, 73% × 1H, J = 6, NH), 6.529 (t, 27% × 1H, J = 6, NH), 4.93-4.61 (m, 7H, sugar-H1 and 3 × $PhCH_2$), 4.14-3.24 (m, 16H, sugar 6 × H, NCH_2CO, 2 × CH_3O [singlets at 3.660 and 3.301, 73%; 3.648 and 3.276, 27%] and ethyl-CH_2), 2.70-2.42 (m, 4H, $COCH_2CH_2CO$), 1.138 (t, 73% × 3H, J = 7, ethyl-CH_3), 1.014 (t, 27% × 3H, J = 7, ethyl-CH_3). ^{13}C (100 MHz, $CDCl_3$, δ 77.0): major rotamer, 173.32, 171.73, 168.94, 138.20, 138.17, 138.09, 128.22, 128.18, 128.10, 127.76, 127.63, 127.49, 127.46, 98.94, 79.97, 75.38, 75.01, 74.84, 73.01, 72.01, 70.10, 54.63, 51.63, 49.84, 43.59, 39.63, 28.99, 27.24, 13.45. minor rotamer (only non-overlapped peaks), 173.26, 171.54, 168.01, 128.27, 127.69, 127.55, 98.98, 79.85, 75.14, 74.40, 72.86, 71.92, 69.97, 54.74, 50.91, 49.72, 42.10, 28.90, 27.83, 12.29.

Step b (PG2068)

Following the general procedure for deprotection of benzyl ethers, a mixture of the above tribenzyl ether (46.8 mg, 0.0706 mmol), 20% palladium on activated charcoal (30 mg) in MeOH (3 mL) was stirred under hydrogen atmosphere at 50 psi for 2 h. General work-up gave

the triol intermediate as a colourless gum. Following the general procedure for sulfonation, the triol was sulfonated (sulfur trioxide trimethylamine complex, 60 °C, 19 h). The residue was dissolved in 1M NaOH (3 mL, 0.16 M). The mixture was stirred at room temperature overnight and concentrated under reduced pressure. The residue was purified via sequential SEC (Bio-Gel P-2 followed by LH20). The pure product was converted into the sodium salt by passing through an ion exchange column to give the PG2068 as a white powder (4.9 mg, 9.8%, two steps). ^{1}H NMR (D_2O, int. ref. acetone at 2.05, 400 MHz): two rotamers in a ratio of 70:30. δ 4.86-4.84 (m, 1H, sugar-H1), 4.69-4.67 (m, 1H, sugar-H2), 4.50-4.46 (m, 1H, sugar-H3), 4.28-4.19 (m, 1H, sugar-H4), 4.072 (s, 30% × 2H, 2H of $COCH_2N$ in minor rotamer), 3.987 (d, 35% × 2H, J= 16.8, 1H of $COCH_2N$ in major rotamer), 3.815 (d, 35% × 2H, J= 16.8, 1H of $COCH_2N$ in major rotamer), 3.79-3.69 (m, 2H, sugar-H5 and one sugar-H6), 3.44-3.18 (m, 6H, one sugar-H6, ethyl-CH_2 and CH_3O [3.245, s, 3H]), 2.633 (t, J= 6.8) and 2.45-2.37 (m, total 4H, $COCH_2CH_2CO_2$), 1.054 (t, 70% × 3H, J= 7.2, CH_3O), 0.906 (t, 30% × 3H, J= 7.2, CH_3O).

Example 12: PG2075

Step a

3-Chlorophenylacetic acid (223 mg, 1.307 mmol) was dissolved in MeCN (3 mL). Ammonia solution (28%, 0.26 mL, 3.8 mmol) was added. The mixture was swirled for a while and evaporated *in vacuo*. The residue was suspended in MeCN (3 mL), filtered and the white solid was washed with MeCN and freeze-dried to afford ammonium 3-chlorophenylacetate (0.195 g, 80%).

Following the general procedure for the Ugi reaction, the above ammonium salt (22.5 mg, 0.120 mmol) and a solution of each following two reagents: formaldehyde (2 M in MeOH, 60 µL, 119 µmol) and *2-isocyanoethyl 2,3,4,6-tetra*-O-*benzyl*-α-D-*mannopyranoside* (0.762 M in $CHCl_3$, 157 µL, 120 µmol) was loaded into a 2 mL sample vial and the mixture stirred at r.t. for 19 h. The volatiles were removed under reduced pressure and the residue purified by flash chromatography to give the product as a colourless gum (34.8 mg, 37%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.39-7.06 (m, 24H, 4 × C_6H_5 and 1 × C_6H_4), 6.731 (t, 1H, J= 6.0, NH), 4.878 (d, 1H, J= 10.8, a-CH_2), 4.844 (d, 1H, J= 2.0, sugar-H1), 4.770 (d, 1H, J= 12.4, b-CH_2), 4.723 (d, 1H, J= 12.4, b-CH_2), 4.640 (s, 2H, c-CH_2), 4.589 (d, 1H, J= 11.6, d-CH_2), 4.535 (d, 1H, J= 11.6, d-CH_2), 4.505 (d, 1H, J= 10.8, a-CH_2), 4.446 (d, 1H, J= 14.8, e-CH_2), 4.362 (d, 1H, J= 14.8, e-CH_2), 3.90-3.51 (m, 12H), 3.38-3.29 (m, 1H). ^{13}C (100 MHz, $CDCl_3$, δ 77.0): 169.67, 166.81, 138.27, 138.11, 137.70, 135.16, 134.31, 129.82, 129.40, 128.34, 128.31, 128.01,

127.85, 127.78, 127.70, 127.68, 127.60, 127.53, 127.46, 98.90, 79.96, 75.08, 75.04, 74.71, 73.58, 72.73, 72.19, 72.13, 69.78, 68.49, 63.17, 40.25, 39.27.

Step b (PG2075)

Following the general procedure for deprotection of benzyl ethers, a mixture of the above tetrabenzyl ether (34.8 mg, 0.0439 mmol), 20% palladium on activated charcoal (26 mg) in MeOH (2 mL) was stirred under hydrogen atmosphere at 50 psi for 2 h. General work-up gave the tetrol intermediate as a colourless gum. Following the general procedure for sulfonation, the above tetrol was sulfonated . The residue was purified via SEC (Bio-Gel P-2). The pure product was converted into the sodium salt by passing through an ion exchange column to give PG2075 as a white fluffy powder after lyophilisation (10.6 mg, 28%, two steps). ^{1}H NMR (D_2O, int. ref. acetone at 2.05, 400 MHz): δ 7.30-7.11 (m, 4H, Ar), 5.00-4.97 (m, 1H, sugar-H1), 4.72-4.28 (m, 3H, sugar-H2, H3 and H4), 4.21-3.30 (m, 11H, sugar-H5, H6 and 4 × CH_2).

Example 13: PG2014

Step a

Following the general procedure for the Ugi reaction, *2-(benzyl3,4,6-tri*-O-*benzyl*-α-D-*mannopyranoside-2-yl)acetic acid* (50 mg, 0.0835 mmol) and a solution of each following three reagents: benzylamine (2 M in MeOH, 41.8 μL, 0.0835 mmol), formaldehyde (2 M in MeOH, 41.8 μL, 0.0835 mmol) and *2-isocyanoethyl 2,3,4,6-tetra*-O-*benzyl*-α-D-*mannopyranoside* (0.415 M in MeOH, 201.4 μL, 0.0835 mmol) was loaded into a 2 mL sample vial and the mixture stirred at r.t. for 19 h. General work-up gave the product as a colourless gum (38.9 mg, 36%). ^{1}H NMR (400 MHz): two rotamers around amide CO-NH single bond in a ratio of 66:34. δ 7.40-7.05 (m, 45H, 9 × C_6H_5), 6.66 (t, 0.66H, J = 5.6, CONH-major rotamer) and 6.40 (t, 0.34H, J = 5.4, CONH-minor rotamer), 5.104 (d, 0.66H, J = 1.2, H1^I-major rotamer) and 5.046 (s, 0.34H, H1^I-minor rotamer), 4.86-4.20 (m, 21H), 3.97-3.48 (m, 16H), 3.36 (q, 0.66H, J = 5.6, major rotamer) and 3.26 (q, 0.34H, J = 5.6, minor rotamer).

Step b (PG2014).

Following the general procedure for the deprotection of benzyl ethers, a mixture of the above octabenzyl ether (35 mg, 0.0267 mmol) and 20% palladium on activated charcoal (10 mg) in EtOH (4 mL) was stirred under hydrogen atmosphere at 50 psi for 2 h. General work-up gave the octol intermediate as a colourless gum. Following the general procedure for sulfonation, the above octol was sulfonated (sulfur trioxide trimethylamine complex, 60 °C, 19 h). The residue was purified via SEC (Bio-Gel P-2). The pure product was converted into the

sodium salt by passing through an ion exchange column to give PG2014 as a white powder (16.6 mg, 44%, two steps). ^{1}H NMR (D_2O, 400 MHz, complicated due to two rotamers): δ 7.32-7.14 (m, 5H, Ph), 5.80-5.66 (m, 0.5H), 5.44-5.39 (m, 0.5H), 5.04-4.96 (m, 1.5H), 4.80-4.20 (m, 9H, overlapped with water), 4.18-3.78 (m, 7.5H), 3.76-3.46 (m, 1.5H), 3.42-2.98 (m, 3.5H).

Example 14: PG2016

Step a

Following the general procedure for the Ugi reaction, *trans*-1,4-diaminocyclohexane (6.3 mg, 0.055 mmol) and a solution of each following three reagents: *2-(methyl 2,3,4-tri*-O-*benzyl*α-D-*mannopyranoside-6-yl)acetic acid* (0.91 M in MeOH, 121 μL, 0.11 mmol), formaldehyde (2 M in MeOH, 55 μL, 0.11 mmol) and cyclohexylisocyanide (1 M in MeOH, 110 μL, 0.11 mmol) was loaded into a 2 mL sample vial and the mixture stirred at r.t. for 5 days. The volatiles were removed under reduced pressure and purified by flash chromatography (gradient elution with hexanes-EtOAc 2:1 to 1:4) to give the product as a colourless gum, 33.0 mg, 43% (Rf = 0.24, DCM-MeOH 95:5 or Rf = 0.48, MeCN-EtOAc 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz, very complicated due to rotamers): δ 7.50-7.20 (m, 30H, Ph), 6.62 (br s, 1.1H), 6.48 (br s, 0.38H), 5.96 (br d, 0.26H, J = 8), 5.79 (br d, 0.26H, J = 10), 4.92-4.85 (m, 2H), 4.78-4.56 (m, 12H), 4.28-4.22 (m, 2.8H), 4.35-4.06 (m, 1.6H), 3.94-3.56 (m, 19.6H), 3.28 (s, 6H, OMe), 1.88-1.42 (m, 16H), 1.36-1.00 (m, 12H).

Step b. (PG2016).

Following the general procedure for the deprotection of benzyl ethers, a mixture of the above hexabenzyl ether (33 mg, 0.0235 mmol) and 20% palladium on activated charcoal (65 mg) in MeOH (2.8 mL) was stirred under hydrogen atmosphere at 1 atm for 5 days. General work-up gave the hexol intermediate as a colourless gum. Following the general procedure for sulfonation, the above hexol was sulfonated. The residue was purified via sequential column chromatography (SEC on Bio-Gel P-2 followed by ion exchange column) to give PG2016 as a white powder (12.2 mg, 35%). ^{1}H NMR (D_2O, 400 MHz): δ 4.97-4.92 (m, 2H, man-H1), 4.77-4.75 (m, 2H, man-H2), 4.58-4.52 (m, 2H, man-H3), 4.46-4.08 (m, 6H, containing man-H4 at 4.46-4.36, and OCH_2CO), 3.98-3.80 (m, 8H, man-H5, man-H6 and NCH_2CO), 3.80-3.32 (m, 6H, containing man-H6 at 3.80-3.64, and cyclohexyl-CH), 3.318 (s, 6H, OMe), 1.82-1.34 (m, 18H, cyclohexyl-CH_2), 1.26-1.00 (m, 10H, cyclohexyl-CH_2). ES-MS (+ve, *m/z*): $C_{40}H_{62}N_4Na_6O_{34}S_6$ required 1472.10, found 1495 ($M+Na^+$), 1473 ($M+H^+$). ES-HRMS (+ve,

m/z): M+Na$^+$, $C_{40}H_{62}N_4Na_7O_{34}S_6$ required 1495.0853, found 1495.0957; M+H$^+$, $C_{40}H_{63}N_4Na_6O_{34}S_6$ required 1473.1034, found 1473.1082.

Example 15: PG2015

Step a

Following the general procedure for the Ugi reaction, 3,3-dimethylglutaric acid (7.1 mg, 0.0443 mmol) and a solution of each following three reagents: *3-aminopropyl 2,3,4,6-tetra-O-benzyl-α-D-mannopyranoside* (0.642 M in MeOH, 138 μL, 0.0886 mmol), formaldehyde (2 M in MeOH, 44.3 μL, 0.0886 mmol) and cyclohexylisocyanide (1 M in MeOH, 88.6 μL, 0..0886 mmol) were loaded into a 2 mL sample vial and the mixture stirred at r.t. for 5 days. The volatiles were removed under reduced pressure and purified by flash chromatography (gradient elution with hexanes-EtOAc 2:1 to 1:4) to give the product as a colourless gum, 32.3 mg, 46% (Rf = 0.45, hexane-EtOAc 1:3). ^{1}H NMR ($CDCl_3$, 400 MHz, very complicated due to rotamers): δ 7.38-7.21 (m, 40H, Ph), 7.003 (d, 0.41H, *J* = 7.7), 6.930 (br s, 0,21H), 6.726 (d, 0.4H, *J* = 8.4), 6.597 (d, 0.73H, *J* = 8.8), 6.487 (br s, 0.25H), 4.85-4.78 (m, 4H), 4.76-4.59 (m, 10H), 4.54-4.45 (m, 4H), 4.00-3.62 (m, 20H), 3.46-3.14 (m, 6H), 2.52-2.22 (m, 4H), 1.90-1.52 (m, 15H), 1.34-1.00 (m, 15H).

Step b (PG2015).

Following the general procedure for the deprotection of benzyl ethers, a mixture of the above hexabenzyl ether (32.3 mg, 0.0202 mmol), 20% palladium on activated charcoal (41 mg) in MeOH (2.8 mL) was stirred under hydrogen atmosphere at 1 atm for 5 days. General work-up gave the octol intermediate as a colourless gum. Following the general procedure for sulfonation, the above octol was sulfonated. The residue was purified via SEC (Bio-Gel P-2) to give PG2015 as a white powder (12.6 mg, 37%). ^{1}H NMR (D_2O, 400 MHz): δ 5.020 (d, 2H, *J* = 1.6, man-H1), 4.759 (br s, 2H, man-H2), 4.66-4.56 (m, 2H, man-H3, overlapped with water), 4.46-4.41 (m, 2H, man-H6), 4.265 (t, 2H, *J* = 9.6, 9.2, man-H4), 4.10-3.96 (m, 4H, man-H5 and man-H6), 4.05-3.14 (m, 14H, NCH_2CO, cyclohexyl-CH and $NCH_2CH_2CH_2O$), 2.50-2.11 (m, 4H, CCH_2CO), 1.84-1.42 (m, 14H, cyclohexyl-CH_2 and $NCH_2CH_2CH_2O$), 1.24-0.93 (m, 16H, cyclohexyl-CH_2 and Me). ES-MS (+ve, *m/z*): $C_{41}H_{93}N_{11}O_{37}S_7$ (7 × SO_3NH_4) required 1556, found 1578 (M+Na$^+$), 1556 (M+H$^+$). ES-HRMS (+ve, *m/z*): M+H$^+$ $C_{41}H_{93}N_{11}O_{37}S_7$ required 1556.3857, found 1556.3783.

Example 16: PG2155.

Ethyl 2,6-Di-O-benzyl-3,4-di-O-sulfo-β-D-galactopyranoside, disodium salt (PG2155)

The title compound was obtained from *ethyl 2,6-di-O-benzyl-3,4-di-O-sulfo-β-D-galactopyranoside* [23] *via* the general sulfonation procedure as a colourless powder. ^{1}H NMR (400 MHz, D_2O) δ 1.10 (dd, 3 H; CH_2CH_3); 2.49-2.66 (m, 2H, CH_2CH_3); 3.59 (dd, 1 H, $J_{1,22,3}$ 9.7 Hz; H-2); 3.65 (dd, 1 H, $J_{5,6a}$ 3.3, $J_{6a,6b}$ 11.0 Hz; H-6a); 3.68 (dd, 1H, $J_{5,6b}$ 4.0 Hz; H-6b); 3.83 (m, 1 H; H-5); 4.36 (dd, 1 H, $J_{3,4}$ 3.0 Hz; H-3); 4.46 (s, 2 H; CH_2Ph); 4.48 (d, 1 H; H-1); 4.60, 4.75 (AB quartet, J 10.3 Hz; CH_2Ph); 4.85 (dd, 1 H; $J_{4,5}$ 0.0 Hz; H-4); 7.22-7.29, 7.37-7.39 (2 m, 10 H; ArH).

Example 17: PG2163.

Step a: Methyl 4-O-allyl-6-azido-6-deoxy-2,3-di-O-isopropylidene-α-D-mannopyranoside

A solution of *methyl 6-azido-6-deoxy-α-D-mannopyranoside* (311 mg, 1.419 mmol) in 2,2-dimethoxypropane (4.7 mL, 0.3 M) was treated with (±)-camphor-10-sulfonic acid (16 mg, 0.0709 mmol, 5 mol%). The mixture was stirred at r.t. for 1 h. TLC indicated the complete conversion to the product (Rf = 0.40, EtOAc-hexane = 17:83). The mixture was basified by addition of sat. Na_2CO_3 (aq. sol.) and evaporated under vacuum. The residue was extracted with EtOAc (30 mL) and the EtOAc solution washed with brine, dried ($MgSO_4$). Filtration and evaporation gave a gum, which was co-evaporated with toluene once. The final colourless gum was dissolved in anhydrous DMF (3.5 mL, 0.4 M) and stirred with NaH (60% dispersion in mineral oil, 163 mg, 4.257 mmol, 3 eq) for 1h. Allyl bromide (360 µL, 4.257 mmol, 3 eq) was added and the mixture stirred at r.t. for another 6 h, treated with methanol (1 mL) and evaporated to dryness. The residue was purified by silica column chromatography (2.5x18 cm, eluted with EtOAc-hexane 1:10 to 1:6) to give the title compound as a colourless gum (0.281 mg, 66% over 2 steps). ^{1}H NMR ($CDCl_3$, 400 MHz): 5.85 (m, 1H, allyl-2'), 5.23 (ddd, 1H, $J_{2\text{-}3'trans}$ = 17.2, $J_{3'\text{-}gem}$ = 3.6, $J_{1'\text{-}3'}$ = 1.6, H3'$_{trans}$), 5.17-5.13 (m, 1H, H3'$_{cis}$), 4.89 (s, 1H, H1), 4.35 (dddd, 1H, $J_{1'gem}$ = 12.4, $J_{1'\text{-}2'}$ = 5.2, J = 1.6, H1'), 4.16 (dd, 1H, $J_{2\text{-}3}$ = 5.6, $J_{3\text{-}4}$ = 7.2, H3), 4.09 (d, 1H, H2), 4.05 (dddd, 1H, H1'), 3.67 (ddd, 1H, $J_{4\text{-}5}$ = 10.4, $J_{5\text{-}6ax}$ = 6.8, $J_{5\text{-}6eq}$ = 2.4, H5), 3.48 (dd, 1H, $J_{6ax\text{-}6eq}$ = 13.2, H6eq), 3.40 (dd, 1H, $J_{6ax\text{-}6eq}$ = 13.2, $J_{5\text{-}6ax}$ = 6.8, H6ax), 3.33 (dd, 1H, H5), 1.50 (s, 3H, Me), 1.30 (s, 3H, Me). ^{13}C NMR ($CDCl_3$, 100 MHz): 134.4, 117.1, 109.2, 98.0, 78.2, 76.2, 75.6, 71.5, 68.0, 54.9, 51.6, 27.8, 26.1.

Step b: Methyl 4-O-allyl-6-azido-6-deoxy-α-D-mannopyranoside

Methyl 4-O-allyl-6-azido-6-deoxy-2,3-di-O-isopropylidene-α-D-mannopyranoside (56 mg, 0.187 mmol) was dissolved in MeCN-MeOH-H_2O (3 mL, 3 mL and 0.2 mL respectively)

and treated with p-toluenesulfonic acid monohydrate (7 mg, 0.0374 mmol, 20 mol%). The mixture was stirred at r.t. for 5 h and triethylamine (0.4 mL) added. The mixture was evaporated and the residue purified by column chromatography (silica 1x18 cm, eluted with EtOAc-hexane 1:6 to 2:1) to give the product as a colourless waxy solid (34.8 mg, 72%). ^{1}H NMR ($CDCl_3$, 400 MHz): 5.91 (m, 1H, allyl-H2'), 5.28 (ddd, 1H, $J_{2'\text{-}3'\text{trans}}$ = 16.8, $J_{3'\text{trans}\text{-}3'\text{cis}}$ = 3.0, $J_{1'\text{-}3'}$ = 1.6, allyl-H3'trans), 5.20 (ddd, 1H, $J_{2'\text{-}3'\text{cis}}$ = 10.0, $J_{3'\text{trans}\text{-}3'\text{cis}}$ = 3.0, $J_{1'\text{-}3'}$ = 1.6, allyl-H3'cis), 4.72 (ddd, 1H, $J_{1\text{-}2}$ = 2.0, H1), 4.28 (dddd, 1H, J_{gem} = 12.4, $J_{1'\text{-}2'}$ = 5.6, J = 1.6, allyl-1'), 4.13 (dddd, 1H, allyl-1'), 3.92 (dd, 1H, $J_{2\text{-}3}$ = 3.6, H2), 3.88 (dd, 1H, $J_{3\text{-}4}$ = 9.6, H3), 3.70 (ddd, 1H, $J_{4\text{-}5}$ = 9.6, $J_{5\text{-}6ax}$ = 5.6, $J_{5\text{-}6eq}$ = 2.8, H5), 3.54-3.44 (m, 3H, H4, H6ax and H6eq), 3.39 (s, 3H, MeO), 2.62 (br s, 2H, OH).

Step c: Methyl 4-O-allyl-6-azido-2-O-benzyl-6-deoxy-2,3-di-O-sulfonato-α-D-mannopyranoside disodium salt (PG2163)

Methyl 4-O-allyl-6-azido-6-deoxy-α-D-mannopyranoside was sulfonated according to the standard procedure to yield the title compound as a white powder, 55 mg (89%). Rf = 0.20 (EtOAc-MeOH-H_2O=10:2:1). ^{1}H NMR (D_2O, 400 MHz): 5.88-5.76 (m, 1H, allyl-2'), 5.20 (d, 1H, $J_{2'\text{-}3'\text{trans}}$ = 17.2, allyl-3'trans), 5.12 (d, 1H, $J_{2'\text{-}3'\text{cis}}$ = 10.0, allyl-3'cis), 4.91 (s, 1H, H1), 4.65 (br s, 1H, $J_{2\text{-}3}$ = 3.2, H2), 4.48 (dd, 1H, $J_{2\text{-}}$ = 3.2, $J_{3\text{-}4}$ = 9.2, H3), 4.21 (dd, 1H, J_{gem} = 11.6, $J_{1'\text{-}2'}$ = 5.6, allyl-1'), 4.00 (dd, 1H, $J_{1'\text{-}2'}$ = 6.4, allyl-1'), 3.71-3.67 (m, 1H, H5), 3.58 (dd, 1H, $J_{6eq\text{-}6ax}$ = 13.6, $J_{5\text{-}6eq}$ = 2.0, H6eq), 3.58 (dd, 1H, $J_{4\text{-}5}$ = 9.6, H4), 3.46 (dd, 1H, $J_{6eq\text{-}6ax}$ = 13.6, $J_{5\text{-}6ax}$ = 5.6, H6ax), 3.30 (s, 3H, MeO). ^{13}C NMR (D_2O, 100 MHz, internal MeOH at 49.05 ppm): 133.9, 119.2, 98.4, 76.1, 75.3, 74.2, 73.1, 70.7, 55.4, 50.8.

Example 18: PG2160, PG2161 and PG2173.

Step a: Methyl 6-azido-6-deoxy-2,3-di-O-benzylidene-α-D-mannopyranoside

Methyl 6-azido-6-deoxy-α-D-mannopyranoside (1.011 g, 4.61 mmol) was dissolved in anhydrous DMF (9 mL) and acetonitrile (9 mL). Benzaldehyde dimethyl acetal (1.38 mL, 9.22 mmol, 2 eq) and (±)-camphor-10-sulfonic acid (214 mg, 0.922 mmol, 20 mol%) were added in that order. The mixture was stirred under house vacuum at 60 °C (external) overnight, and the volatile materials were removed on rotavap. The residue was loaded on silica gel and purified by column (silica 2.5x20 cm, gradient elution with hexane-ethyl aceate 10:1, 9:1, 7:1, 5:1, 4:1, 3:1 to 2:1). The fractions were pooled into two parts. The less polar part (Rf = 0.55 and 0.51, hexane-EtOAc 3:1) was a mixture of 4-acetals and the polar part was mainly the 4-OH product. The mixtures were combined and evaporated. The residue was re-dissolved in dichloromethane (50 mL) and stirred with 1M ammonium chloride solution (50 mL). The less

polar spots were slowly disappeared and converted into the polar product. However, the conversion was not further improved after 40 min. Thus the dichloromethane phase was separated and stirred with 0.5 M HCl solution (50 mL) for another 20 min. TLC indicated no further change. The DCM phase was separated and washed with brine-1M NaOH, dried ($MgSO_4$). The dried DCM solution was filtered, evaporated and the residue was purified by silica column as above to give the title compound as a colourless gummy solid (0.543 g, 38%, Rf = 0.29, EtOAc-hexane = 1:3). ^1H NMR ($CDCl_3$, 400 MHz): two benzylidene epimers in a ratio of 1:1. 7.49-7.36 (m, 5H, C_6H_5), 6.126 and 5.902 (2xs, 1H, benzylidene-CH), 5.066 and 4.987 (2xs, 1H, sugar-H1), 4.396 (dd, 0.5H, J = 6.4, 5.6, sugar-H3), 4.248 (dd, 0.5H, J = 6.4, 6.0, sugar-H3), 4.214 (dd, 0.5H, J = 6.0, sugar-H2), 4.102 (dd, 0.5H, J = 4.8, sugar-H2), 3.86-3.38 (m, 4H), 3.466 and 3.424 (2xs, 3H, CH_3O), 2.984 (br s, 1H, OH). ^{13}C NMR ($CDCl_3$, 100 MHz): 138.01, 136.41, 129.38, 128.99, 128.24, 128.12, 126.41, 125.86, 103.85, 102.60, 97.74, 97.53, 79.36, 77.75, 77.47, 74.81, 70.00, 68.91, 68.42, 66.97, 54.78, 51.18 and 51.10.

Step b: Methyl 6-azido-3-O-benzyl-6-deoxy-α-D-mannopyranoside and methyl 6-azido-2-O-benzyl-6-deoxy-α-D-mannopyranoside

A solution of methyl 6-azido-6-deoxy-2,3-di-*O*-benzylidene-α-D-mannopyranoside (240 mg, 0.781 mmol) in DMF (7.8 mL, 0.1 M) was treated with sodium cyanoborohydride (589 mg, 9.37 mmol, 12 eq) and molecular sieve 3Å (1 g). The mixture was stirred at r.t. for 20 min, then at 70 °C while TFA (0.361 mL, 4.686 mmol, 6 eq) was added slowly. After addition, the mixture was stirred at 70 °C for 6 h, cooled to 0 °C and basified by addition of solid Na_2CO_3. The cold mixture was filtered and the cake washed with EtOAc. The filtrate and washings was extracted once with sat. Na_2CO_3. Evaporation gave a gum, which was purified by column chromatography (silica 2.5x18 cm, eluted with EtOAc-hexane 1:4 to 1:1) to give *methyl 6-azido-3-O-benzyl-6-deoxy-α-D-mannopyranoside* (colourless gum, 64 mg, 26%, Rf = 0.45, EtOAc-hexane=1:1); ^1H NMR ($CDCl_3$, 400 MHz): 7.41-7.32 (m, 5H, Ph), 4.78 (d, 1H, J_{1-2} = 1.6, H1), 4.70 (d, 1H, J_{gem} = 12.0, CH_2), 4.56 (d, 1H, CH_2), 4.02 (dd, 1H, J_{2-3} = 3.2, H2), 3.78 (dd, 1H, J_{3-4} = 8.4, J_{4-5} = 10.0, H4), 3.73 (ddd, 1H, J_{5-6ax} = 6.0, J_{5-6eq} = 3.2, H5), 3.64 (dd, 1H, H3), 3.52 (dd, 1H, $J_{6ax-6eq}$ = 13.2, H6eq), 3.47 (dd, 1H, $J_{6ax-6eq}$ = 13.2, J_{5-6ax} = 6.0, H6ax), 3.40 (s, 3H, MeO), 2.21 (br s, 2H, 2xOH) and *methyl 6-azido-2-O-benzyl-6-deoxy-α-D-mannopyranoside* (colourless waxy solid, 62 mg, 26%, Rf = 0.27, EtOAc-hexane=1:1). ^1H NMR ($CDCl_3$, 400 MHz): 7.38-7.28 (m, 5H, Ph), 4.78 (s, 1H, H1), 4.71 (d, 1H, J = 11.6, CH_2), 4.53 (d, 1H, J = 11.6, CH_2), 3.75-3.61 (m, 4H, H2, H3, H4 and H5), 3.53 (dd, 1H, J = 13.2, 1.5, H6eq), 3.46-3.40 (dm, 1H, J = 13.2, H6ax), 3.38 (s, 3H, MeO), 2.83 (br s, 2H, 2xOH).

Step c: Methyl 6-azido-2-O-benzyl-6-deoxy-2,3-di-O-sulfonato-α-D-mannopyranoside disodium salt (PG2160)

Methyl 6-azido-2-O-benzyl-6-deoxy-α-D-mannopyranoside was sulfonated according to the standard procedure to yield the title compound as a white powder, 64 mg, 59%. ^{1}H NMR (D_2O, 400 MHz): 7.38-7.26 (m, 5H, Ph), 4.72 (d, 1H, J_{gem} = 12.0, CH_2Ph), 4.59 (d, 1H, J_{1-2} = 2.0, H1), 4.58 (d, 1H, CH_2Ph), 4.49 (d, 1H, J_{2-3} = 2.8, J_{3-4} = 9.6, H3), 4.44 (dd, 1H, J_{4-5} = 9.6, H4), 4.07 (dd, 1H, H2), 3.78 (ddd, 1H, J_{5-6ax} = 5.6, J_{5-6eq} = 2.4, H5), 3.62 (dd, 1H, $J_{6ax-6eq}$ = 13.2, H6eq), 3.51 (dd, 1H, $J_{6ax-6eq}$ = 13.2, J_{5-6ax} = 5.6, H6ax), 3.22 (s, 3H, MeO).

Step d: Methyl 6-azido-3-O-benzyl-6-deoxy-2,4-di-O-sulfonato-α-D-mannopyranoside disodium salt (PG2161)

Methyl 6-azido-3-O-benzyl-6-deoxy-α-D-mannopyranoside (64 mg) was sulfonated according to the standard procedure to yield the title compound as a white powder, 58 mg, 66%. ^{1}H NMR (D_2O, 400 MHz): 7.42-7.21 (m, 5H, Ph), 4.92 (d, 1H, J_{1-2} = 2.4, H1), 4.67 (d, 1H, J_{gem} = 12.4, CH_2Ph), 4.60 (d, 1H, CH_2Ph), 4.56 (dd, 1H, J_{2-3} = 3.2, H2), 4.35 (dd, 1H, J_{3-4} = 9.6, J_{4-5} = 9.6, H4), 3.80 (dd, 1H, H3), 3.75 (ddd, 1H, J_{5-6ax} = 6.0, J_{5-6eq} = 2.8, H5), 3.66 (dd, 1H, $J_{6ax-6eq}$ = 13.4, H6eq), 3.54 (dd, 1H, $J_{6ax-6eq}$ = 13.4, J_{5-6ax} = 6.0, H6ax), 3.29 (s, 3H, MeO).

Step e: Methyl 6-[1'-(4-phenyl)triazolyl]-2-O-benzyl-6-deoxy-2,3-di-O-sulfonato-α-D-mannopyranoside disodium salt (PG2173)

Methyl 6-azido-2-O-benzyl-6-deoxy-2,3-di-O-sulfonato-α-D-mannopyranoside disodium salt was subjected to the Huisgen reaction general procedure using phenyl acetylene to yield the title compound as a white powder 6.8 mg, 67%, Rf = 0.34, EtOAc-MeOH-H_2O = 10:2:1. ^{1}H NMR (D_2O, 400 MHz): 8.26 (s, 1H, triazole), 7.64-7.60 (m, 2H), 7.37-7.15 (m, 8H), 4.89 (dd, 1H, J = 14.4, 2.8, H3), 4.67 (d, 1H, J = 12.0, $PhCH_2$), 4.57-4.39 (m, 5H, $PhCH_2$, H1, H4 and H6eq and H6ax), 4.04 (dd, 1H, J = 2.8, 2.0, H2), 3.99 (ddd, 1H, J = 9.2, 8.8, 2.4, H5), 2.83 (s, 3H, MeO).

Example 19: PG2170

Allyl 6-azido-2,3-O-disulfonato-6-deoxy-4-O-(1-naphthylmethyl)-α-D-mannopyranoside disodium salt (containing 10% of 2-naphthylmethyl isomer) (PG2170)

The title compound, prepared analogously to PG2163 beginning with *allyl 6-azido-6-deoxy-α-D-mannopyranoside,* was obtained as a white powder 87.5 mg, 87%, Rf = 0.28 (major), 0.22 (minor), EtOAc-MeOH-H_2O = 10:2:1. ^{1}H NMR (D_2O, 400 MHz): 7.87 (d, 1H, J = 8.4, naphthyl), 7.65-7.54 (m, 2H, naphthyl), 7.33-7.19 (m, 4H, naphthyl), 5.68 (ddt, 1H, $J_{allyl2'-3'trans}$ = 22.0, $J_{allyl2'-3'cis}$ = 10.8, $J_{allyl1'-2'}$ = 6.0, allyl-2'), 5.23 (AB quartet, 2H, J_{gem} = 12.0,

naphthyl-CH_2), 5.17-5.02 (m, 3H, allyl-3' and H1), 4.74 (dd, 1H, J_{1-2} = 2.0, J_{2-3} = 3.2, H2), 4.64 (d, 1H, J_{3-4} = 9.6, H3), 3.90 (dd, 1H, $J_{allyl1'gem}$ = 13.2, J = 6.0, allyl-1'), 3.81 (dd, 1H, allyl-1'), 3.64 (t, 1H, J_{4-5} = 9.6, H4), 3.39 (ddd, 1H, J_{5-6eq} = 2.0, J_{5-6ax} = 5.2, H5), 2.78 (dd, 1H, $J_{6eq-6ax}$ = 13.6, H6eq), 2.68 (dd, 1H, J_{5-6ax} = 5.2, $J_{6eq-6ax}$ = 13.6, H6ax). Typical signals for minor isomer 2-naphthylmethyl derivative: 4.84 (AB quartet, 2H, J_{gem} = 11.2, naphthyl-CH_2), 3.52 (ddd, 1H, J_{4-5} = 10.0, J_{5-6eq} = 2.4, J_{5-6ax} = 6.0, H5), 3.07 (dd, 1H, $J_{6eq-6ax}$ = 13.6, H6eq), 2.96 (dd, 1H, $J_{6eq-6ax}$ = 13.6, J_{5-6ax} = 6.0, H6ax). The source of the minor isomer is the commercial 9:1 mixture of 1- and 2-bromomethylnapthalene used in step a.

Additional compounds were synthesized using appropriate modifications of the syntheses detailed above in Examples 1 to 19. These additional compounds are included in the tables giving the results of biological testing of compounds according to the invention.

Example 20

Biological Testing of Compounds

Methods

1. Growth Factor Binding

Binding affinities of ligands for the growth factors were measured using a surface plasmon resonance (SPR) based solution affinity assay. The principle of the assay is that heparin immobilised on a sensorchip surface distinguishes between free and bound growth factor in an equilibrated solution of the growth factor and a ligand. Upon injection of the solution, the free growth factor binds to the immobilised heparin, is detected as an increase in the SPR response and its concentration thus determined. A decrease in the free growth factor concentration as a function of the ligand concentration allows for the calculation of the dissociation constant, K_d. It is important to note that ligand binding to the growth factors can only be detected when the interaction involves the heparin binding site, thus eliminating the chance of evaluating non-specific binding to other sites on the protein. A 1:1 stoichiometry has been assumed for all protein:ligand interactions.

The preparation of heparin-coated sensorchips, via immobilisation of biotinylated BSA-heparin on a streptavidin-coated sensorchip, has been described [24]. Heparin has also been immobilised via aldehyde coupling using either adipic acid dihydrazide or 1,4-diaminobutane. For each K_d measurement, solutions were prepared containing a fixed concentration of protein and varying concentrations of the ligand in buffer. Ligands binding to FGF-1 and VEGF were measured in HBS-EP buffer (10 mM HEPES, pH 7.4, 150 mM NaCl, 3.0 mM EDTA and 0.005% (v/v) polysorbate 20), while binding to FGF-2 was measured in HBS-EP buffer

containing 0.3 M NaCl [24]. Prior to injection, samples were maintained at 4 °C to maximise protein stability. For each assay mixture, 50-200 µL of solution was injected at 5-40 µL/min and the relative binding response measured. All surface binding experiments were performed at 25 °C. The surface was regenerated by injection of 40 µL of 4M NaCl at 40 µL/min, followed by injection of 40 µL of buffer at 40 µL/min.

Sensorgram data were analysed using the BIAevaluation software (BIAcore). Background sensorgrams were subtracted from experimental sensorgrams to produce curves of specific binding, and baselines were subsequently adjusted to zero for all curves. The relative binding response for each injection was converted to free protein concentration using the equation

$$[P]=\frac{r}{r_m}[P]_{total}$$

where r is the relative binding response and r_m is the maximal binding response.

Binding equilibria established in solution prior to injection were assumed to be of 1:1 stoichiometry. Therefore, for the equilibrium,

$$P + L \rightleftharpoons P{\cdot}L$$

where P corresponds to the growth factor protein, L is the ligand, and $P{\cdot}L$ is the protein:ligand complex, the equilibrium equation is

$$K_d = \frac{[P][L]}{[P \cdot L]}$$

and the binding equation [24] can be expressed as

$$[P]=[P]_{total}-\frac{(K_d+[L]_{total}+[P]_{total})}{2}+\sqrt{\frac{(K_d+[L]_{total}+[P]_{total})^2}{4}-[L]_{total}[P]_{total}}$$

The K_d values given are the values fit, using the binding equation, to a plot of $[P]$ versus $[L]_{total}$. Where K_d values were measured in duplicate, the values represent the average of the duplicate measurements. It has been shown that GAG mimetics that bind tightly to these growth factors elicit a biological response *in vivo* [24].

2. Antiviral Assays.

Selected compounds were tested against two types of herpes simplex virus (HSV), i.e.,

HSV-1 and HSV-2, in two assays for inhibition of viral infectivity and cell-to-cell spread, as described by Nyberg et al. [25]. Monolayer cultures of African green monkey kidney cells (GMK AH1) [26] cultivated in 6-well cluster plates, were used. The viral strains used were herpes simplex virus type 1 (HSV-1) KOS321 strain [27] and HSV-2 strain 333 [28].

In both assays the compounds were tested at 200 μM.

(i) In the assay of HSV infectivity, the compounds were mixed with the virus, incubated for 10 min at room temperature and then the mixture was added to cells, and kept on cells for 1h only to allow (or not) the virus attachment to/entry into the cells. Thus this assay reflects whether or not the compound in question has the ability to bind to the virus particles and block its attachment to/entry into the cells. An inhibition is manifested as a decreased number of viral plaques.

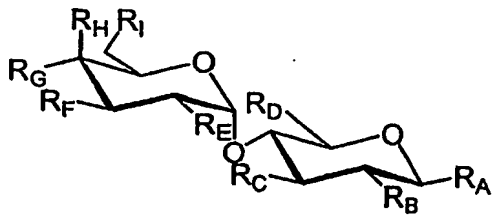
(ii) The next assay, termed HSV spread, relies on the addition of compound to the cells after the virus attachment/entry steps have already occurred. This assay reflects whether the examined compound has the ability to inhibit virus transmission from an infected to an uninfected cell (cell-to-cell spread) and in addition whether the compound has the ability to enter the cells and inhibit viral replication. Lack of compound activity in the assay of virus infectivity but some activity in the virus spread assay suggests that the compound acts by entering the cells and inhibition of viral replication step(s). An inhibition is manifested as a reduction in the size of viral plaques.

The results (see Table 5) are expressed as % of control, ie., as the number (infectivity assay) or the size (spread assay) of viral plaques developed in the presence of compound relative to the mock-treated controls (no compound).

Results

The results of the tests as described in the preceding section are presented in Tables 1 to 5.

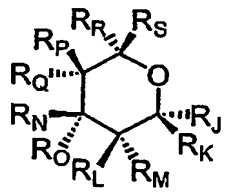
Table 1



III

	PG #	Kd aFGF	Kd bFGF	Kd VEGF	Kd FGF-4
R_A,R_F,R_H,R_I=OMe; R_B,R_C,R_E=OSO_3Na; R_D=CH_2OSO_3Na; R_G=H	2019	218 μM	657 μM		912 μM
R_A,R_F,R_H=OMe; R_B,R_C,R_E,R_I=OSO_3Na; R_D=CH_2OSO_3Na; R_G=H	2037	47.7 μM	507 μM	645 μM	
R_F,R_H,R_I=OH; R_A=OMe; R_B,R_C,R_E=OSO_3Na; R_D=CH_2OSO_3Na; R_G=H	2038	77.9 μM	2.10 mM	368 μM	
R_A=OMe; R_F,R_H=OH; R_B,R_C,R_E,R_I=OSO_3Na; R_D=CH_2OSO_3Na; R_G=H	2039	21.8 μM	3.50 mM	1.27 mM	
R_F,R_G,R_I=OH; R_D-R_A=-CH_2O-; R_B,R_E=$NHSO_3Na$; R_C=OBn; R_H=H	2046	6.35 mM	3.70 mM	1.50 mM	
R_F,R_G,R_I,R_C=OH; R_D-R_A=-CH_2O-; R_B,R_E=$NHSO_3Na$; R_H=H	2047	388 μM	1.95 mM	2.55 mM	
R_F,R_H,R_I=OH; R_A=OMe; R_B,R_C,R_E=OSO_3Na; R_D,R_G=H	2063	1.39 mM	2.35 mM	2.59 mM	

Table 2



IV

	PG #	Kd aFGF	Kd bFGF	Kd VEGF
R_K=OMe; R_M,R_O=OSO_3Na; R_Q=OBn; R_R=CH_3; R_J,R_L,R_N,R_P,R_S=H	2023	1.76 mM	4.90 mM	2.27 mM
R_K=OMe; R_M,R_O=OSO_3Na; R_P=OBn; R_R=CH_3; R_J,R_L,R_N,R_Q,R_S=H	2024	4.73 mM	3.65 mM	6.40 mM
R_K=OMe; R_M,R_N=OBz; R_Q=OSO_3Na; R_S=CH_2OSO_3Na; R_J,R_L,R_O,R_P,R_R=H	2028	1.10 mM	9.25 mM	>> 1.65 mM
R_K=OMe; R_M,R_O=OSO_3Na; R_Q=Oallyl; R_R=CH_3; R_J,R_L,R_N,R_P,R_S=H	2029	1.34 mM	> 10.00 mM	236 μM
R_S-R_K= -CH_2O-; R_M=OSO_3Na; R_N=OMe; R_Q=OBn; R_J,R_L,R_O,R_P,R_R=H	2030	317 μM	4.61 mM	
R_N=$O(CH_2)_3OPh$;R_Q=OSO_3Na; R_S=CH_2OSO_3Na; R_J,R_K,R_L,R_M,R_O,R_P,R_R=H	2040	12.9 mM	7.50 mM	2.44 mM
R_N=OBn;R_Q=OSO_3Na; R_S=CH_2OSO_3Na; R_J,R_K,R_L,R_M,R_O,R_P,R_R=H	2041	9.38 mM	5.10 mM	1.04 mM
R_K=OMe; R_M=OSO_3Na; R_O=OH; R_P=Oallyl; R_R=CH_3; R_J,R_L,R_N,R_Q,R_S=H	2042	3.05 mM	10.7 mM	2.59 mM

	PG #	Kd aFGF	Kd bFGF	Kd VEGF
R_N=OMe;R_Q=OSO_3Na; R_S=CH_2OSO_3Na; R_J,R_K,R_L,R_M,R_O,R_P,R_R=H	2043	6.43 mM	17.4 mM	1.73 mM
R_K =OMe; R_M,R_Q=OSO_3Na; R_P=$OOCCH_2CH_2Ph$; R_R=CH_3; R_J,R_L,R_N,R_Q,R_S=H	2044	366 μM	1.55 mM	1.65 mM
R_J/R_K=H/OMe (anomeric mixture); R_S-R_N= -CH_2O-; R_M=OSO_3Na; R_Q=OBn; R_L,R_O,R_P,R_R=H	2045	392 μM	3.40 mM	1.07 mM
R_K=OMe; R_N,R_M=OH; R_Q=OSO_3Na; R_S=CH_2OSO_3Na; R_J,R_L,R_O,R_P,R_R=H	2048	233 μM	5.30 mM	796 μM
R_K=OMe; R_N,R_M=OBn; R_Q=OSO_3Na; R_S=CH_2OSO_3Na; R_J,R_L,R_O,R_P,R_R=H	2049	1.51 mM	>> 60.0 μM	2.72 mM
R_K=OMe; R_M =OSO_3Na; R_N,R_Q=OBn; R_J,R_L,R_O,R_P,R_R,R_S=H	2050	3.31 mM	8.25 mM	~ 10.00 mM
R_K=OMe; R_M,R_N=OBn; R_Q=OSO_3Na; R_J,R_L,R_O,R_P,R_R,R_S=H	2051	2.46 mM	> 20.4 mM	4.63 mM
R_K=OMe; R_M,R_O=OSO_3Na; R_P=$OOCCH_2OPh$; R_R=CH_3; R_J,R_L,R_N,R_Q,R_S=H	2052	5.92 mM	4.50 mM	686 μM
R_K=OMe; R_M,R_O=OSO_3Na; R_P=Oallyl; R_R=CH_3; R_J,R_L,R_N,R_Q,R_S=H	2053	1.30 mM	5.17 mM	343 μM
R_K=OMe; R_M,R_O=OSO_3Na; R_P=OBz; R_R=CH_3; R_J,R_L,R_N,R_Q,R_S=H	2054	454 μM	2.73 mM	403 μM
R_K=OMe; R_M,R_O=OSO_3Na; R_P=OOCPh(*p*-OMe); R_R=CH_3; R_J,R_L,R_N,R_Q,R_S=H	2056	797 μM	2.45 mM	485 μM
R_S-R_N= -CH_2O-; R_L=OSO_3Na; R_Q=OBn; R_J,R_K,R_M,R_O,R_P,R_R=H	2079	1.92 mM	~ 3.45 mM	1.73 mM
R_S-R_N= -CH_2O-; R_M=OSO_3Na; R_Q=OBn; R_J,R_K,R_L,R_O,R_P,R_R=H	2080	1.62 mM	~ 11.7 mM	1.36 mM
R_K=OMe; R_M,R_O=OSO_3Na; R_P=OCH_2Cyclohexyl; R_R=CH_3; R_J,R_L,R_N,R_Q,R_S=H	2085	9.60 mM	~ 17.4 mM	8.90 mM
R_K=OMe; R_M,R_O=OSO_3Na; R_P=$O(CH_2)_3OPh$; R_R=CH_3; R_J,R_L,R_N,R_Q,R_S=H	2086		3.05 mM	1.50 mM
R_K=OMe; R_M,R_O=OSO_3Na; R_P=OH; R_R=CH_3; R_J,R_L,R_N,R_Q,R_S=H	2087	566 μM	2.35 mM	899 μM
R_K=OMe; R_M,R_O=OSO_3Na; R_P=$O(CH_2)_3Ph$; R_R=CH_3; R_J,R_L,R_N,R_Q,R_S=H	2088	676 μM	3.00 mM	761 μM
R_K=OMe; R_M,R_O=OSO_3Na; R_P=OCH_2(2-Napthyl); R_R=CH_3; R_J,R_L,R_N,R_Q,R_S=H	2089	1.20 mM	2.15 mM	2.33 mM
R_K=OMe; R_M,R_O=OSO_3Na; R_P=OCH_2(*E*)CH=CHPh; R_R=CH_3; R_J,R_L,R_N,R_Q,R_S=H	2090	3.85 mM	2.50 mM	3.02 mM
R_K=OMe; R_M,R_O=OSO_3Na; R_P=OCH_2(1-Napthyl); R_R=CH_3; R_J,R_L,R_N,R_Q,R_S=H	2091	1.37 mM	1.50 mM	1.98 mM

	PG #	Kd aFGF	Kd bFGF	Kd VEGF
R_K=OMe; R_M,R_O=OSO_3Na; R_P=OCH_2Ph(*p*-Me); R_R=CH_3; R_J,R_L,R_N,R_Q,R_S=H	2092	2.70 mM	2.85 mM	2.86 mM
R_K=OMe; R_M,R_O=OSO_3Na; R_P=OOCPh(*p*-NO_2); R_R=CH_3; R_J,R_L,R_N,R_Q,R_S=H	2093	110 μM	1.66 mM	856 μM
R_K=NHCOCH_2OPh(2,4-di-Cl); R_M,R_N,R_O=OSO_3Na; R_S=CH_2OSO_3Na; R_J,R_L,R_O,R_P,R_R=H	2096	35.7 μM	141 μM	20.4 μM
R_J=OMe; R_L,R_N=OBz; R_Q=OSO_3Na; R_S=CH_2OSO_3Na; R_K,R_M,R_O,R_P,R_R=H	2097	127 μM	2.05 mM	267 μM
R_K=OMe; R_M,R_O=OSO_3Na; R_P=OCH_2Ph(*p*-CF_3); R_R=CH_3; R_J,R_L,R_N,R_Q,R_S=H	2098	~7.85 mM	2.65 mM	2.60 mM
R_K=OMe; R_M,R_O=OSO_3Na; R_P=OCH_2Ph(*m*-CF_3); R_R=CH_3; R_J,R_L,R_N,R_Q,R_S=H	2099	1.30 mM	2.85 mM	5.70 mM
R_J=OMe; R_L,R_Q=OSO_3Na; R_N=Oallyl; R_S=CH_2Oallyl; R_K,R_M,R_O,R_P,R_R=H	2100	1.25 mM	~18.1 mM	146 μM
R_J=OMe; R_L,R_N=OH; R_Q=OSO_3Na; R_S=CH_2OSO_3Na; R_K,R_M,R_O,R_P,R_R=H	2101	77.3 μM		188 μM
R_K=OMe; R_M,R_O=OSO_3Na; R_P=OMe; R_R=CH_3; R_J,R_L,R_N,R_Q,R_S=H	2102	116 μM	1.30 mM	206 μM
R_K=OMe; R_M,R_O=OSO_3Na; R_P=OCH_2Cyclopropyl; R_R=CH_3; R_J,R_L,R_N,R_Q,R_S=H	2103	5.50 mM	4.20 mM	3.00 mM
R_K=N_3; R_M,R_O=OSO_3Na; R_P=OBn; R_R=CH_3; R_J,R_L,R_N,R_Q,R_S=H	2104	1.80 mM	2.45 mM	3.30 mM
R_J=N_3; R_M=OSO_3Na;R_O=OH; R_P=OBn; R_R=CH_3; R_K,R_L,R_N,R_Q,R_S=H	2105	1.85 mM	2.10 mM	8.30 mM
R_K=OBn; R_M,R_O=OSO_3Na; R_P=OMe; R_R=CH_3; R_J,R_L,R_N,R_Q,R_S=H	2106	1.31 mM	3.43 mM	1.45 mM
R_K=OMe; R_M,R_N=OOCPh(*p*-OMe); R_Q=OSO_3Na; R_S=CH_2OSO_3Na; R_J,R_L,R_O,R_P,R_R=H	2107	645 μM		
R_K=OMe; R_M,R_N=OCH_2(*E*)CH=CHPh; R_Q=OSO_3Na; R_S=CH_2OSO_3Na; R_J,R_L,R_O,R_P,R_R=H	2108		563 μM	
R_K=OMe; R_M,R_N=OOCPh(*p*-NO_2); R_Q=OSO_3Na; R_S=CH_2OSO_3Na; R_J,R_L,R_O,R_P,R_R=H	2109	441 μM		1.00 mM
R_K-R_S=-OCH_2-; R_M=3-phenyl-[1,2,3]triazol-1-yl; R_N,R_Q=OSO_3Na; R_J,R_L,R_O,R_P,R_R=H	2110	2.80 mM		
R_K=OMe; R_M,R_O=OSO_3Na; R_P=OOCPh(3,4-di-Cl); R_R=CH_3; R_J,R_L,R_N,R_Q,R_S=H	2111	1.30 mM		1.60 mM
R_K=OMe; R_M,R_O=OSO_3Na; R_P=OOCCH_2Ph(*m*-Cl); R_R=CH_3; R_J,R_L,R_N,R_Q,R_S=H	2112	2.30 mM	2.55 mM	4.10 mM
R_K=OMe; R_M,R_O=OSO_3Na; R_P=OOCCH_2Ph(3,4-di-Cl); R_R=CH_3; R_J,R_L,R_N,R_Q,R_S=H	2113	1.45 mM	1.60 mM	1.60 mM

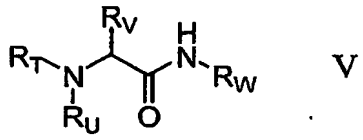
	PG #	Kd aFGF	Kd bFGF	Kd VEGF
R_K=OMe; R_M,R_Q=OSO_3Na; R_P=$OOCCH_2Ph(p\text{-}CF_3)$; R_R=CH_3; R_J,R_L,R_N,R_Q,R_S=H	2114	3.85 mM	2.30 mM	888 µM
R_J=OMe; R_L=OMe; R_N=Oallyl; R_Q=OSO_3Na; R_S=CH_2OSO_3Na; R_K,R_M,R_O,R_P,R_R=H	2129	5.40 mM	9.10 mM	3.00 mM
R_J=OMe; R_L,R_N=OSO_3Na; R_Q=OMe; R_S=CH_2Oallyl; R_K,R_M,R_O,R_P,R_R=H	2130	1.05 mM	7.85 mM	361 µM
R_K=OMe; R_M,R_Q=OSO_3Na; R_P=OEt; R_R=CH_3; R_J,R_L,R_N,R_Q,R_S=H	2131	8.30 mM	7.20 mM	~21.8 mM
R_J=OMe; R_L,R_N,R_Q=OAc; R_S=CH_2OSO_3Na; R_K,R_M,R_O,R_P,R_R=H	2137	> 20.0 mM		~8.80 mM
R_J=OMe; R_L,R_Q=OSO_3Na; R_N=Oallyl; R_S=$CH_2OC(Ph_3)$; R_K,R_M,R_O,R_P,R_R=H	2139	884 µM	~2.70 mM	383 µM
R_J=OMe; R_L=OSO_3Na; R_N=Oallyl; R_Q=$OCH_2(CH_3)C{=}CH_2$; R_S=$CH_2OCH_2(CH_3)C{=}CH_2$; R_K,R_M,R_O,R_P,R_R=H	2140	1.90 mM		862 µM
R_J=OMe; R_L,R_Q=OSO_3Na; R_N=Oallyl; R_S=CH_2OMe; R_K,R_M,R_O,R_P,R_R=H	2141	4.90 mM		613 µM
R_J=OMe; R_L,R_Q=OSO_3Na; R_N=Oallyl; R_S=$CH_2OCH_2(CH_3)C{=}CH_2$; R_K,R_M,R_O,R_P,R_R=H	2142	3.00 mM		481 µM
R_K=Oallyl; R_M=OMe;R_N=4-phenyl-[1,2,3]triazol-1-yl,R_Q=OSO_3Na; R_S=CH_2OSO_3Na; R_J,R_L,R_O,R_P,R_R=H	2143	1.10 mM		398 µM
R_K=$NHCOCH_2O$Ph(2,4-di-Cl); R_M,R_N,R_Q=OH; R_S=CH_2OSO_3Na; R_J,R_L,R_O,R_P,R_R=H	2144	6.00 mM		3.00 mM
R_J=OMe; R_L,R_Q=OSO_3Na; R_N=Oallyl; R_S=CH_2OH; R_K,R_M,R_O,R_P,R_R=H	2145	~5.95 mM	~23.0 mM	1.60 mM
R_J=OMe; R_L,R_Q=OSO_3Na; R_N=Oallyl; R_S=CH_2OBn; R_K,R_M,R_O,R_P,R_R=H	2147	1.50 mM	9.10 mM	2.10 mM
R_J=OMe; R_L,R_Q=OSO_3Na; R_N=Oallyl; R_S=CH_2OCH_2(3-pyridyl); R_K,R_M,R_O,R_P,R_R=H	2148	2.40 mM	~13.0 mM	981 µM
R_J=OMe; R_L,R_Q=OSO_3Na; R_N=OCH_2(2-napthyl); R_S=CH_2OH; R_K,R_M,R_O,R_P,R_R=H	2149	2.50 mM	~6.70 mM	709 µM
R_J=OMe; R_L,R_Q=OSO_3Na; R_N=OBn; R_S=CH_2OH; R_K,R_M,R_O,R_P,R_R=H	2150	>> 6.00 mM	~24.2 mM	7.80 mM
R_J=OMe; R_L,R_Q=OSO_3Na; R_N=OBn; R_S=CH_2Oallyl; R_K,R_M,R_O,R_P,R_R=H	2151	3.50 mM	~9.90 mM	935 µM
R_K=OMe; R_M,R_Q=OSO_3Na; R_P=OPr; R_R=CH_3; R_J,R_L,R_N,R_Q,R_S=H	2152	~6.30 mM		3.40 mM
R_J=OMe; R_L,R_Q=OH; R_N=OSO_3Na; R_S=CH_2N_3; R_K,R_M,R_O,R_P,R_R=H	2153	~11.5 mM	>> 42.1 mM	~11.1 mM
R_J=OMe; R_L,R_N=-OCHPhO-; R_Q=OSO_3Na; R_S=CH_2N_3; R_K,R_M,R_O,R_P,R_R=H	2154	~3.70 mM	~26.7 mM	2.15 mM

	PG #	Kd aFGF	Kd bFGF	Kd VEGF
R_K=SEt; R_M=OBn; R_N,R_P=OSO_3Na; R_S=CH_2OBn; R_J,R_L,R_O,R_Q,R_R=H	2155	188 μM	1.06 mM	448 μM
R_J=OMe; R_L,R_Q=OSO_3Na; R_N=Oallyl; R_S=CH_2N_3; R_K,R_M,R_O,R_P,R_R=H	2156	360 μM	1.65 mM	1.04 mM
R_J=OMe; R_L,R_N=OSO_3Na; R_Q=OBn; R_S=CH_2N_3; R_K,R_M,R_O,R_P,R_R=H	2157	444 μM	3.30 mM	144 μM
R_J=OMe; R_L=OH;R_N=OSO_3Na; R_Q=OCH_2(2-napthyl); R_S=CH_2N_3; R_K,R_M,R_O,R_P,R_R=H	2158	1.55 mM	~ 10.3 mM	985 μM
R_J=OMe; R_L,R_Q=OH; R_N=OSO_3Na; R_S=CH_2NH_2; R_K,R_M,R_O,R_P,R_R=H	2159	1.90 mM	~ 62.3 mM	6.40 mM
R_J=OMe; R_L=OBn; R_N,R_Q=OSO_3Na; R_S=CH_2N_3; R_K,R_M,R_O,R_P,R_R=H	2160	4.40 mM	2.50 mM	~ 12.9 mM
R_J=OMe; R_L,R_Q=OSO_3Na; R_N=OBn; R_S=CH_2N_3; R_K,R_M,R_O,R_P,R_R=H	2161		~ 18.2 mM	~ 10.6 mM
R_J=OMe; R_L,R_N=OSO_3Na; R_Q=Oallyl; R_S=CH_2N_3; R_K,R_M,R_O,R_P,R_R=H	2163	396 μM	4.80 mM	61.2 μM
R_J=OMe; R_L,R_N=OSO_3Na; R_Q=OCH_2(2-napthyl); R_S=CH_2N_3; R_K,R_M,R_O,R_P,R_R=H	2164	1.35 mM	1.70 mM	1.30 mM
R_J/R_K=H/OMe (anomeric mixture); R_S-R_N= -CH_2O-; R_M=OBn; R_Q=OSO_3Na; R_J,R_K,R_L,R_O,R_P,R_R=H	2165	1.13 mM	~ 25.5 mM	1.70 mM
R_K=SMe; R_M,R_O=OSO_3Na; R_P=OBn; R_R=CH_3; R_J,R_L,R_N,R_Q,R_S=H	2166	3.60 mM	1.90 mM	2.70 mM
R_K=OBn; R_M,R_O=OSO_3Na; R_P=OBn; R_R=CH_3; R_J,R_L,R_N,R_Q,R_S=H	2168	1.90 mM		1.20 mM
R_J=Oallyl; R_L,R_N=OSO_3Na; R_Q=OCH_2(1-napthyl); R_S=CH_2N_3; R_K,R_M,R_O,R_P,R_R=H	2170	277 μM	1.35 mM	106 μM
R_J=OMe; R_L,R_Q=OSO_3Na; R_N=OBn; R_S=CH_2NH_2; R_K,R_M,R_O,R_P,R_R=H	2171	845 μM	~ 18.9 mM	2.00 mM
R_J=OMe; R_L=OBn; R_N,R_Q=OSO_3Na; R_S=CH_2NH_2; R_K,R_M,R_O,R_P,R_R=H	2172	3.80 mM	~ 5.90 mM	2.30 mM
R_J=OMe; R_L=OBn; R_N,R_Q=OSO_3Na; R_S=CH_2(4-phenyl-[1,2,3]triazol-1-yl); R_K,R_M,R_O,R_P,R_R=H	2173	18.9 μM	918 μM	89.3 μM
R_J=Oallyl; R_L=OH; R_N=OSO_3Na; R_Q=OBz; R_S=CH_2N_3; R_K,R_M,R_O,R_P,R_R=H	2174	278 μM	~ 19.3 mM	846 μM
R_J=OMe; R_L,R_N=OSO_3Na; R_Q=Oallyl; R_S=CH_2NH_2; R_K,R_M,R_O,R_P,R_R=H	2175	465 μM		136 μM
R_J=OMe; R_L,R_N=OSO_3Na; R_Q=Oallyl; R_S=CH_2(4-(CH_2NH_2)-[1,2,3]triazol-1-yl); R_K,R_M,R_O,R_P,R_R=H	2176	693 μM		256 μM
R_K=OMe; R_M,R_O=OSO_3Na; R_P=OCO-Cyclohexyl; R_R=CH_3; R_J,R_L,R_N,R_Q,R_S=H	2177	~ 9.40 mM		

	PG #	Kd aFGF	Kd bFGF	Kd VEGF
R_J=OMe; R_L,R_N=OSO_3Na; R_Q=Oallyl; R_S=CH_2(4-(CH_2NHCO(2-napthyl))-[1,2,3]triazol-1-yl); R_K,R_M,R_O,R_P,R_R=H	2178	130 µM	1.20 mM	60.9 µM
R_J=OMe; R_L,R_N=OSO_3Na; R_Q=Oallyl; R_S=CH_2(4-(CH_2NHCO-Cyclohexyl)-[1,2,3]triazol-1-yl); R_K,R_M,R_O,R_P,R_R=H	2179	52.9 µM	143 µM	10.3 µM
R_J=OMe; R_L,R_N=OSO_3Na; R_Q=Oallyl; R_S=CH_2(4-(CH_2NHCO-Ph(*p*-OMe))-[1,2,3]triazol-1-yl); R_K,R_M,R_O,R_P,R_R=H	2180	91.9 µM		1.90 mM
R_J=OMe; R_L,R_N=OSO_3Na; R_Q=Oallyl; R_S=CH_2(4-($CH_2NHCOCH_2OPh$)-[1,2,3]triazol-1-yl); R_K,R_M,R_O,R_P,R_R=H	2181	365 µM		203 µM
R_J=OMe; R_L,R_N=OSO_3Na; R_Q=Oallyl; R_S=CH_2(4-($CH_2NHCOPh$)-[1,2,3]triazol-1-yl); R_K,R_M,R_O,R_P,R_R=H	2182	107 µM		847 µM
R_J=OMe; R_L,R_N=OSO_3Na; R_Q=Oallyl; R_S=CH_2(4-(CH_2-*N*-phthalimido)-[1,2,3]triazol-1-yl); R_K,R_M,R_O,R_P,R_R=H	2183	324 µM		82.7 µM
R_J=OMe; R_L,R_N=OSO_3Na; R_Q=Oallyl; R_S=CH_2(4-(CH_2NHSO_2Ph(*p*-Me))-[1,2,3]triazol-1-yl); R_K,R_M,R_O,R_P,R_R=H	2184	388 µM		1.6 mM
R_J=OMe; R_L,R_N=OSO_3Na; R_Q=Oallyl; R_S=CH_2(4-Ph-[1,2,3]triazol-1-yl); R_K,R_M,R_O,R_P,R_R=H	2185	421 µM		440 µM
R_J=OMe; R_L,R_N=OSO_3Na; R_Q=Oallyl; R_S=CH_2(4-*t*-butyl-[1,2,3]triazol-1-yl); R_K,R_M,R_O,R_P,R_R=H	2186	88.6 µM		>4.6 mM
R_J=OMe; R_L=OSO_3Na; R_N=OH; R_Q=OCH_2(2-napthyl); R_S=CH_2N_3; R_K,R_M,R_O,R_P,R_R=H	2187	320 µM		
R_J=OMe; R_L,R_N=OSO_3Na; R_Q=OCH_2(2-napthyl); R_S=CH_2N_3; R_K,R_M,R_O,R_P,R_R=H	2188	1.22 mM		821 µM
R_J=OMe; R_L,R_N=OSO_3Na; R_Q=Oallyl; R_S=CH_2NHSO_2Me; R_K,R_M,R_O,R_P,R_R=H	2189	191 µM		35.0 µM
R_J=OMe; R_L,R_N=OSO_3Na; R_Q=Oallyl; R_S=$CH_2NHCOCH_3$; R_K,R_M,R_O,R_P,R_R=H	2190	408 µM		98.0 µM
R_J=OMe; R_L,R_N=OSO_3Na; R_Q=Oallyl; R_S=CH_2NHBz; R_K,R_M,R_O,R_P,R_R=H	2191	1.39 mM		317 µM
R_J=OMe; R_L,R_N=OSO_3Na; R_Q=Oallyl; R_S=$CH_2NHCOPh$(*p*-OMe); R_K,R_M,R_O,R_P,R_R=H	2192	1.85 mM		222 µM
R_J=OMe; R_L,R_N=OSO_3Na; R_Q=Oallyl; R_S=CH_2(4-(CH_2NHCO(o-CO_2Na)phenyl)-[1,2,3]triazol-1-yl); R_K,R_M,R_O,R_P,R_R=H	2193	1.20 mM		270 µM
R_J=OMe; R_L,R_N=OSO_3Na; R_Q=Oallyl; R_S=CH_2(4-($CH_2NHCOPh$(3,4,5-tri-OMe))-[1,2,3]triazol-1-yl); R_K,R_M,R_O,R_P,R_R=H	2194	1.25 mM		>2.8 mM
R_J=OPh(*p*-OMe); R_L,R_N=OSO_3Na; R_Q=OBn; R_S=CH_2N_3; R_K,R_M,R_O,R_P,R_R=H	2195	1.05 mM		751 µM

	PG #	Kd aFGF	Kd bFGF	Kd VEGF
R_K=OBn; R_M,R_O=OSO_3Na; R_P=OBn; R_R=CH_3; R_J,R_L,R_N,R_Q,R_S=H	2196	170 μM		2.50 mM
R_J=OMe; R_L,R_N=OSO_3Na; R_Q=Oallyl; R_S=CH_2(4-(CH_2OCH_2Ph(*p*-OMe))-[1,2,3]triazol-1-yl); R_K,R_M,R_O,R_P,R_R=H	2197	131 μM		381 μM

Table 3



V

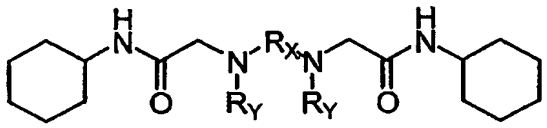
	PG #	Kd aFGF	Kd bFGF	Kd VEGF
R_T=1,2,3,4-tetra-*O*-sodium sulfonato-D-glucuronoyl; R_U=$CH_2CH_2OSO_3Na$; R_W=cyclohexyl; R_V=H	2007	2.34 mM		
R_T=1-*O*-Me-2,3,4-tri-*O*-sodium sulfonato-α-D-mannopyranos-6-yl-acetyl; R_U=$CH_2CH_2OSO_3Na$; R_V=H ; R_W=cyclohexyl	2008	296 μM	551 μM	335 μM
R_T=Ac; R_U=2-(2,3,4,6-tetra-*O*-sodium sulfonato-α-D-mannopyranos-1-*O*-yl-)-ethyl; R_V=H; R_W=2-(2,3,4,6-tetra-*O*-sodium sulfonato-α-D-mannopyranos-1-*O*-yl-)-ethyl	2009	428 μM		
R_T=3-(2,3,4,6-tetra-*O*-sodium sulfonato-α-D-mannopyranos-1-*O*-yl-)-propyl; R_U=$COCH_2CH_2Ph$; R_W=cyclohexyl; R_V=H	2010	556 μM		
R_T=1,2,3,4-tetra-*O*-sodium sulfonato-D-glucuronoyl; R_U=Bn; R_W=cyclohexyl; R_V=Ph	2011	62.4 μM		
R_T=1,2,3,4-tetra-*O*-sodium sulfonato-α-D-glucuronoyl; R_U=Bn; R_W=cyclohexyl; R_V=H	2012	122 μM	505 μM	
R_T=1,2,3-tri-*O*-sodium sulfonato-α-D-glucuronoyl; R_U=Bn; R_W=cyclohexyl; R_V=H	2013	587 μM	1.16 mM	
R_T=1,3,4,6-tetra-*O*-sodium sulfonato-α-D-mannopyranos-2-yl-acetyl; R_U=Bn; R_V=H; R_W=2-(2,3,4,6-tetra-*O*-sodium sulfonato-α-D-mannopyranos-1-*O*-yl-)-ethyl	2014	5.09 μM	85.1 μM	8.82 μM
R_T=3-(2,3,4,6-tetra-*O*-sodium sulfonato-α-D-mannopyranos-1-*O*-yl-)-propyl; R_U= $CO(CH_2)_3Ph$; R_V=H; R_W=cyclohexyl	2018			
R_T=1,2,3,4-tetra-*O*-sodium sulfonato-α-D-glucuronoyl; R_U,R_W=Bn; R_V=H	2020	104 μM	206 μM	437 μM
R_T=1-*O*-Me-2,3,4-tri-*O*-sodium sulfonato-α-D-mannopyranos-6-yl-acetyl; R_U=Bn; R_W=cyclohexyl; R_V=H	2032	260 μM	201 μM	705 μM

	PG #	Kd aFGF	Kd bFGF	Kd VEGF
R_T=1-*O*-Me-2,3,4-tri-*O*-sodium sulfonato-α-D-mannopyranos-6-yl-acetyl; R_U=Bn; R_V=H; R_W=2-(2,3,4,6-tetra-*O*-sodium sulfonato-α-D-mannopyranos-1-*O*-yl-)-ethyl	2034	37.6 μM	16.5 μM	115 μM
R_T=Ac; R_U=Bn; R_V=H; R_W=2-(2,3,4,6-tetra-*O*-sodium sulfonato-α-D-mannopyranos-1-*O*-yl-)-ethyl	2035	24.8 μM	287 μM	76.6 μM
R_T=Ac; R_U=Bn; R_V=H; R_W=2-(2,3,4,6-tetra-*O*-sodium sulfonato-β-D-mannopyranos-1-*O*-yl-)-ethyl	2036	118 μM	2.50 mM	1.10 mM
R_T=Ac; R_U=CH_2CH_2Ph; R_V=H; R_W=6-deoxy-1-*O*-Me-2,3,4-tri-*O*-sodium sulfonato-α-D-mannopyranos-6-yl	2058	224 μM	682 μM	109 μM
R_T=Ac; R_U=CH_2CH_2Ph; R_V=H; R_W=6-deoxy-1-*O*-Me-2,3,4-tri-*O*-sodium sulfonato-α-D-mannopyranos-6-yl	2058	224 μM	682 μM	109 μM
R_T=Ac; R_U=Bn; R_V=H; R_W=6-deoxy-1-*O*-Me-2,3,4-tri-*O*-sodium sulfonato-α-D-mannopyranos-6-yl	2059	140 μM	192 μM	77.0 μM
R_T=Ac; R_U=Bn; R_V=H; R_W=6-deoxy-1-*O*-Me-2,3,4-tri-*O*-sodium sulfonato-α-D-mannopyranos-6-yl	2059	140 μM	192 μM	77.0 μM
R_T=Ac; R_U=Ph; R_V=H; R_W=6-deoxy-1-*O*-Me-2,3,4-tri-*O*-sodium sulfonato-α-D-mannopyranos-6-yl	2060	196 μM	481 μM	76.3 μM
R_T=Ac; R_U=cyclohexyl; R_V=H; R_W=6-deoxy-1-*O*-Me-2,3,4-tri-*O*-sodium sulfonato-α-D-mannopyranos-6-yl	2064	314 μM	413 μM	1.70 mM
R_T=Ac; R_U=$CH_2CH_2OSO_3Na$; R_V=H; R_W=6-deoxy-1-*O*-Me-2,3,4-tri-*O*-sodium sulfonato-α-D-mannopyranos-6-yl	2065	94.8 μM	241 μM	283 μM
R_T=m-$ClPhCH_2CO$; R_U=H; R_V=H; R_W=6-deoxy-1-*O*-Me-2,3,4-tri-*O*-sodium sulfonato-α-D-mannopyranos-6-yl	2066	37.4 μM	433 μM	45.3 μM
R_T=Et; R_U=$CO(CH_2)_2COONa$; R_V=H; R_W=6-deoxy-1-*O*-Me-2,3,4-tri-*O*-sodium sulfonato-α-D-mannopyranos-6-yl	2068	338 μM	291 μM	207 μM
R_T=Et; R_U=$CO(CH_2)_WCOONa$; R_V=H; R_W=6-deoxy-1-*O*-Me-2,3,4-tri-*O*-sodium sulfonato-α-D-mannopyranos-6-yl	2069	160 μM	477 μM	104 μM
R_T=Et; R_U=$CO(CH_2)_9OSO_3Na$; R_V=H; R_W=6-deoxy-1-*O*-Me-2,3,4-tri-*O*-sodium sulfonato-α-D-mannopyranos-6-yl	2070	111 μM	243 μM	545 μM
R_T=Et; R_U=$CO(CH_2)_WCOONa$; R_V=H; R_W=6-deoxy-1-*O*-Me-2,3,4-tri-*O*-sodium sulfonato-α-D-mannopyranos-6-yl, mixture of mono- and di- sulfates	2071	119 μM	2.24 mM	161 μM
R_T=Ac; R_U=cyclohexyl; R_V=H; R_W=6-deoxy-1-*O*-Me-2,3,4-tri-*O*-sodium sulfonato-α-D-mannopyranos-6-yl, mixture of mono- and di-sulfates	2072	264 μM	2.98 mM	277 μM
R_T=Ac; R_U=Ph; R_V=H; R_W=2-(2,3,4,6-tetra-*O*-sodium sulfonato-α-D-mannopyranos-1-*O*-yl-)-ethyl	2073	97.4 μM	236 μM	402 μM
R_T=Ac; R_U=$(CH_2)_2Ph$; R_V=H; R_W=2-(2,3,4,6-tetra-*O*-sodium sulfonato-α-D-mannopyranos-1-*O*-yl-)-ethyl	2074	11.8 μM	113 μM	28.8 μM
R_T= m-$ClPhCH_2CO$; R_U,R_V=H; R_W=2-(2,3,4,6-tetra-*O*-sodium sulfonato-α-D-mannopyranos-1-*O*-yl-)-ethyl	2075	171 μM	837 μM	90.8 μM

	PG #	Kd aFGF	Kd bFGF	Kd VEGF
R_T=Et; R_U=$CO(CH_2)_2CO_2Na$; R_V=H; R_W=2-(2,3,4,6-tetra-*O*-sodium sulfonato-α-D-mannopyranos-1-*O*-yl-)-ethyl	2076	43.4 μM	118 μM	40.3 μM
R_T=Et; R_U=$CO(CH_2)_4CO_2Na$; R_V=H; R_W=2-(2,3,4,6-tetra-*O*-sodium sulfonato-α-D-mannopyranos-1-*O*-yl-)-ethyl	2077	43.6 μM	188 μM	81.1 μM
R_T=Et; R_U=$CO(CH_2)_9OSO_3Na$; R_V=H; R_W=2-(2,3,4,6-tetra-*O*-sodium sulfonato-α-D-mannopyranos-1-*O*-yl-)-ethyl	2078	20.0 μM	157 μM	49.6 μM
R_T=Bz; R_U=Et; R_V=H; R_W=6-deoxy-1-*O*-Me-2,3,4-tri-*O*-sodium sulfonato-α-D-mannopyranos-6-yl	2081	366 μM	480 μM	1.10 mM
R_T=$CO(CH_2)_2Ph$; R_U=Et; R_V=H; R_W=6-deoxy-1-*O*-Me-2,3,4-tri-*O*-sodium sulfonato-α-D-mannopyranos-6-yl	2082			596 μM
R_T=$CO(CH_2)_3Ph$; R_U=Et; R_V=H; R_W=6-deoxy-1-*O*-Me-2,3,4-tri-*O*-sodium sulfonato-α-D-mannopyranos-6-yl	2083	453 μM	403 μM	80.7 μM
R_T=$COCH_2OSO_3Na$; R_U=Et; R_V=H; R_W=6-deoxy-1-*O*-Me-2,3,4-tri-*O*-sodium sulfonato-α-D-mannopyranos-6-yl	2084	161 μM	192 μM	277 μM
R_W=cyclohexyl; R_U=Ac; R_V=H; R_T=6-deoxy-1-*O*-Me-2,3,4-tri-*O*-sodium sulfonato-α-D-mannopyranos-6-yl	2094	246 μM	565 μM	1.10 mM
R_W=cyclohexyl; R_U=Ac; R_V=H; R_T=6-deoxy-1-*O*-Me-2,3-*O*-benzylidene,4-*O*-sodium sulfonato-α-D-mannopyranos-6-yl	2115	5.10 mM		3.90 mM
R_T=Ac; R_U=cycloheptyl; R_V=H; R_W=6-deoxy-1-*O*-Me-2,3,4-tri-*O*-sodium sulfonato-α-D-mannopyranos-6-yl	2116	369 μM	411 μM	3.00 mM
R_T=Ac; R_U=cycloheptyl; R_V=H; R_W=6-deoxy-1-*O*-Me-2,4-di-*O*-sodium sulfonato-α-D-mannopyranos-6-yl	2117	1.50 mM		2.90 mM
R_T=Ac; R_U=cyclooctyl; R_V=H; R_W=6-deoxy-1-*O*-Me-2,4-di-*O*-sodium sulfonato-α-D-mannopyranos-6-yl	2120	1.60 mM	~ 11.0 mM	
R_T=$COCH_2Ph(p\text{-}CF_3)$; R_U=Et; R_V=H; R_W=6-deoxy-1-*O*-Me-2,4-di-*O*-sodium sulfonato-α-D-mannopyranos-6-yl	2122	3.70 mM		1.20 mM
R_T=$COCH_2Ph(p\text{-}CF_3)$; R_U=Et; R_V=H; R_W=6-deoxy-1-*O*-Me-2,3-di-*O*-sodium sulfonato-α-D-mannopyranos-6-yl	2124	242 μM		570 μM
R_W=cyclohexyl; R_U=Ac; R_V=H; R_T=6-deoxy-1-*O*-Me-4-*O*-sodium sulfonato-α-D-mannopyranos-6-yl	2125	26.6 mM		~ 166 mM
R_T=Ac; R_U=cyclododecyl; R_V=H; R_W=6-deoxy-1-*O*-Me-2,3,4-tri-*O*-sodium sulfonato-α-D-mannopyranos-6-yl	2126	265 μM	483 μM	1.20 mM
R_T=Ac; R_U=4-t-butylcyclohexyl; R_V=H; R_W=6-deoxy-1-*O*-Me-2,3,4-tri-*O*-sodium sulfonato-α-D-mannopyranos-6-yl	2132	243 μM	544 μM	1.00 mM
R_T=Ac; R_U=1-(1-adamantyl)-ethyl; R_V=H; R_W=6-deoxy-1-*O*-Me-2,4-di-*O*-sodium sulfonato-α-D-mannopyranos-6-yl	2133	398 μM		
R_T=$CO(CH_2)_3Ph$; R_U=Et; R_V=H; R_W=6-deoxy-1-*O*-Me-2,4-di-*O*-sodium sulfonato-α-D-mannopyranos-6-yl	2135			

	PG #	Kd aFGF	Kd bFGF	Kd VEGF
R_T=6-deoxy-1-*O*-Me-2,3,4-tri-*O*-sodium sulfonato-α-D-mannopyranos-6-yl; R_U=CH_2CONHcyclohexyl; R_W=cyclohexyl; R_V=H	2138	418 μM	449 μM	1.34 mM
R_W=cyclohexyl; R_U=CHO; R_V=H; R_T=6-deoxy-1-*O*-Me-2,3,4-tri-*O*-sodium sulfonato-α-D-mannopyranos-6-yl	2162			1.20 mM

Table 4



VI

	PG #	Kd aFGF	Kd bFGF	Kd VEGF
R_X=$COCH_2C(CH_3)_2CH_2CO$; R_Y=3-(2,3,4,6-tetra-*O*-sodium sulfo-α-D-mannopyranos-1-O-yl)-propyl	2015	2.94 μM	7.56 μM	267 nM
R_X=1,4-*trans*-cyclohexyl; R_Y=1-O-Me-2,3,4-tri-*O*-sodium sulfo-α-D-mannopyranos-6-yl-acetyl	2016	32.6 μM	81.8 μM	931 nM
R_X=$COCH_2C(CH_3)_2CH_2CO$; R_Y=2-(2,3,4,6-tetra-*O*-sodium sulfo-α-D-mannopyranos-1-O-yl)-ethyl, undersulfated	2057	18.8 μM	61.6 μM	55.6 μM
R_X=$COCH_2C(CH_3)_2CH_2CO$; R_Y=2-(2,3,4,6-tetra-*O*-sodium sulfo-α-D-mannopyranos-1-O-yl)-ethyl	2062	10.3 μM	29.7 μM	17.3 μM

Table 5: Antiviral Testing Results

PG#	HSV-1 Infectivity	HSV-2 Infectivity	HSV-1 Spread	HSV-2 Spread
2000	100.8	NT (= not tested)	82.1	NT
2001	85.6	NT	88.3	NT
2002	89.2	NT	113.8	NT
2003	97	NT	95.2	NT
2005	102.8	NT	131.7	NT
2040	106.6	NT	86.2	NT
2041	108.3	NT	60	NT
2042	92	NT	107.6	NT

PG#	HSV-1 Infectivity	HSV-2 Infectivity	HSV-1 Spread	HSV-2 Spread
2000	100.8	NT (= not tested)	82.1	NT
2001	85.6	NT	88.3	NT
2002	89.2	NT	113.8	NT
2003	97	NT	95.2	NT
2005	102.8	NT	131.7	NT
2040	106.6	NT	86.2	NT
2041	108.3	NT	60	NT
2044	73.5	NT	77.9	NT
2085	99.2	NT	64.1	52.8
2091	81.8	135.6	74.9	58.9
2092	90.3	101.4	75.4	50
2093	90.3	121.6	74.9	55.5
2097	101.8	111.5	45	42.2
2098	81.8	116.3	68.4	54.4
2099	89.5	115.9	76	43.3
2103	80.8	112	94.2	70
2111	100.3	105.3	57.9	55.5
2112	95.6	90.9	74.9	76.7
2113	95.1	91.3	46.2	31.1
2114	86.4	99	71.3	68.9
2139	86.8	81.8	47.8	20
2146	108.5	92	56.2	52.8
2145	92.1	76	73.7	77.8
2151	100	75.5	84.5	86.1

The results presented in Tables 1 to 4 demonstrate that the broad range of compounds embraced by the invention have strong affinity for GAG-binding growth factors and may thus serve as modulators of their activity. The results in presented in Table 5 demonstrate that the compounds do indeed possess in vivo activity.

The foregoing embodiments are illustrative only of the principles of the invention, and various modifications and changes will readily occur to those skilled in the art. The invention is capable of being practiced and carried out in various ways and in other embodiments. It is also to be understood that the terminology employed herein is for the purpose of description and should not be regarded as limiting.

The term "comprise" and variants of the term such as "comprises" or "comprising" are used herein to denote the inclusion of a stated integer or stated integers but not to exclude any other integer or any other integers, unless in the context or usage an exclusive interpretation of the term is required.

Any reference to publications cited in this specification is not an admission that the disclosures constitute common general knowledge in Australia.

REFERENCES

[1] Kjellen, L.; Lindahl, U. *Annu. Rev. Biochem.* **1991**, *60*, 443.

[2] Sugahara, K.; Kitagawa, H. *Curr. Opin. Struct. Biol.* **2000**, *10*, 518.

[3] 20179369 Tumova, S.; Woods, A.; Couchman, J.R. *Int. J. Biochem. Cell Biol.* **2000**, *32*, 269.

[4] Capila, I.; Linhardt, R.J. *Angew. Chem. Int. Ed.* **2002**, *41*, 391.

[5] Casu, B.; Lindahl, U. *Adv. Carbohydr. Chem. Biochem.* **2001**, *57*, 159.

[6] Liu, J.; Thorp, S.C. *Med. Res. Rev.* **2002**, *22*, 1.

[7] van Boeckel, C.A.A.; Petitou, M. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1671.

[8] Petitou, M.; Hérault, J.P.; Bernat, A.; Driguez, P.A.; Duchaussoy, P.; Lormeau, J.C.; Herbert, J.M. *Nature* **1999**, *398*, 417.

[9] Yeh, B.K.; Eliseenkova, A.V.; Plotnikov, A.N.; Green, D.; Pinnell, J.; Polat, T.; Gritli-Linde, A.; Linhardt, R.J.; Mohammadi, M. *Mol. Cell. Biol.* **2002**, *22*, 7184.

[10] Liekens, S.; Leali, D.; Neyts, J.; Esnouf, R.; Rusnati, M.; Dell Era, P.; Maudgal, P.C.; De Clercq, E.; Presta, M. *Mol. Pharmacol.* **1999**, *56*, 204.

[11] Sola, F.; Farao, M.; Pesenti, E.; Marsiglio, A.; Mongelli, N.; Grandi, M. *Cancer Chemother. Pharmacol.* **1995**, *36*, 217.

[12] Foxall, C.; Wei, Z.; Schaefer, M.E.; Casabonne, M.; Fugedi, P.; Peto, C.; Castellot, J.J., Jr; Brandley, B.K. *J. Cell. Physiol.* **1996**, *168*, 657.

[13] Parish, C.R.; Freeman, C.; Brown, K.J.; Francis, D.J.; Cowden, W.B. *Cancer Res.* **1999**, *59*, 3433.

[14] Kisilevsky, R.; Green, A.M.; Gervais, F. **2001**, *US Patent No.* 6,310,073.

[15] Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168 and references cited therein.

[16] Lockhoff, O.; Frappa, I. *Combinatorial Chemistry & High Throughput Screening* **2002**, *5*, 361 and references cited therein.

[17] Hanessian, S. *Preparative Carbohydrate Chemistry*; Chapter 3; Marcel Dekker Inc.: New York, **1996**.

[18] Pozsgay, V.; Trinh, L.; Shiloach, J.; Robbins, J.B.; Donohue-Rolfe, A.; Calderwood, S.B. *Bioconjugate Chem.* **1996**, *7*, 45.

[19] Dasgupta, F.; Masada, R.I. *Carbohydr. Res.* **2002**, *337*, 1055.

[20] Hori, H.; Nishida, Y.; Ohrui, H.; Meguro, H. *J. Org. Chem.* **1989**, *54*, 1346.

[21] Prepared analogously to ref. 18.

[22] Lipták, A.; Imre, J.; Nánási, P. *Carbohydr. Res.* **1981**, *92*, 154.

[23] Ágoston, K.; Kerékgyártó, J.; Hajkó, J.; Batta, G.; Lefeber, D.J.; Kamerling, J.P.; Vliegenthart, J.F. *Chem. Eur. J.* **2002**, *8*, 151.

[24] Cochran, S.; Li, C.; Fairweather, J.K.; Kett, W.C.; Coombe, D.R.; Ferro, V. *J. Med. Chem.* **2003**, *46*, 4601.

[25] Nyberg, K.; Ekblad, M.; Bergström, T.; Freeman, C.; Parish, C.R.; Ferro, V.; Trybala, E. *Antiviral Res.* **2004**, *63*, 15.

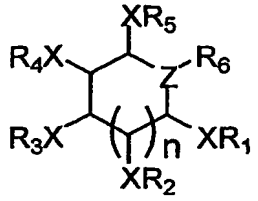
[26] Gunalp, A. *Proc. Soc. Exp. Biol. Med.* **1965**, *118*, 185.

[27] Holland, T.C.; Homa, F.L.; Marlin, S.D.; Levine, M.; Glorioso, J. *J. Virol.* **1984**, *52*, 566.

[28] Duff, R.; Rapp, F. *Nat. New Biol.* **1971**, *233*, 48.

CLAIMS

1. A compound of the formula



I

wherein:

n is an integer of from 0 to 2;

Z is N, N(O), O, S, S(O), $S(O)_2$, P, P(O), $P(O)_2$, Si, Si(O), or $Si(O)_2$;

each X is independently C, C(O), N, N(O), O, S, S(O), $S(O)_2$, P, P(O), $P(O)_2$, Si, Si(O), or $Si(O)_2$ or is a bond; and

each of R_1 to R_6 is independently a bond or is selected from the group consisting of:

hydrogen;

halogen;

straight chain, cyclic, branched, substituted, heterocyclic, heteroatom substituted or unsubstituted alkyl, alkenyl, alkynyl, aryl, or heteroaryl;

phosphoryl groups such as phosphate, thiophosphate -O-P(S)$(OH)_2$; phosphate esters -O-P(O)$(OR)_2$; thiophosphate esters -O-P(S)$(OR)_2$; phosphonate -O-P(O)OHR; thiophosphonate -O-P(S)OHR; substituted phosphonate -O-P(O)OR_1R_2; substituted thiophosphonate -O-P(S)OR_1R_2; -O-P(S)(OH)(SH); and cyclic phosphate;

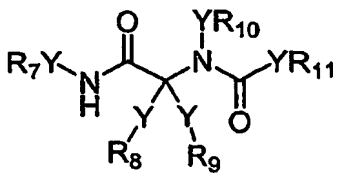
other phosphorus containing compounds such as phosphoramidite -O-P(OR)-NR_1R_2; and phosphoramidate -O-P(O)(OR)-NR_1R_2;

sulfur groups such as -O-S(O)(OH), -SH, -SR, -S(→O)-R, $S(O)_2R$, RO-$S(O)_2$-, -O-SO_2NH_2, -O-$SO_2R_1R_2$ or sulfamide –$NHSO_2NH_2$;

amino groups such as –NHR, -NR_1R_2, -NHAc, -NHCOR, -NH-O-COR, -$NHSO_3$, -$NHSO_2R$, -$N(SO_2R)_2$, and/or amidino groups such as -NH-C(=NH)NH_2 and/or ureido groups such as -NH-CO-NR_1R_2 or thiouriedo groups such as –H-C(S)-NH_2;

another unit of the structure I, attached through any position, where Z, X and R_1 to R_6 are as defined above; or

a substructure based upon a group of the following formula:



II

wherein:

Y is a bond or is selected from the group consisting of: straight chain, cyclic, branched, substituted, heterocyclic, heteroatom substituted or unsubstituted alkyl; straight chain, cyclic, branched, substituted, heterocyclic, heteroatom substituted or unsubstituted acyl; and aryl, substituted aryl, heteroaryl;

and

each of R_7 to R_{11} is independently at least one structure according to formula **I**, or a structure according to formula **II**;

with the provisos that:

when Z is O, and X is O or a bond, then all of R_1 to R_5 are not H or CH_2OH; or

when Z is N and X is O or a bond, then all of R_1 to R_6 are not H.

2. A compound according to claim 1, wherein said compound is PG2024, PG2037, PG2046, PG2155, as hereinbefore described.

3. A compound according to claim 1, wherein said compound is any one of the compounds of Tables 1-4 of the description.

4. A pharmaceutical or veterinary composition for the prevention or treatment in a mammalian subject of a disorder resulting from angiogenesis, metastasis, inflammation, coagulation, thrombosis, and/or microbial infection, which composition comprises at least one compound according to claim 1 together with a pharmaceutically or veterinarially acceptable carrier or diluent for said at least one compound.

5. The composition according to claim 4 which further includes a pharmaceutically or veterinarially acceptable excipient, buffer, stabiliser, isotonicising agent, preservative or antioxidant.

6. The composition according to claim 4, wherein said compound is present therein as an ester, a free acid or base, a hydrate, or a prodrug.

7. Use of a compound according to claim 1 in the manufacture of a medicament for the prevention or treatment in a mammalian subject of a disorder resulting from angiogenesis, metastasis, inflammation, coagulation, thrombosis, and/or microbial infection.

8. The use according to claim 7, wherein said mammalian subject is a human subject.

9. A method for the prevention or treatment in a mammalian subject of a disorder resulting from angiogenesis, metastasis, inflammation, coagulation, thrombosis, and/or microbial infection, which method comprises administering to the subject an effective amount of at least one compound according to claim 1, or a composition comprising said at least one compound.

10. The method according to claim 9 wherein said mammalian subject is a human subject.

11. The method according to claim 9, wherein said disorder resulting from angiogenesis is a proliferative retinopathy or angiogenesis resulting from the growth of a solid tumour.

12. The method according to claim 9, wherein said disorder resulting from inflammation is rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, allograft rejection or chronic asthma.

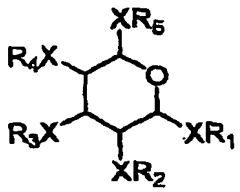
13. The method according to claim 9, wherein said disorder resulting from coagulation and/or thrombosis is deep venous thrombosis, pulmonary embolism, thrombotic stroke, peripheral arterial thrombosis, unstable angina or myocardial infarction.

14. The method according to claim 9, wherein said disorder resulting from viral infection is Herpes Simplex.

AMENDED CLAIMS

[(received by the International Bureau on 11 May 2005 (11.05.05); original claims 1-2 amended; remaining claims unchanged (3 pages)]

1. A compound of the formula



I

wherein:

each X is independently CH_2, C(O), N, O, S, S(O), $S(O)_2$, or is a bond; and

each of R_1 to R_5 is independently a bond or is selected from the group consisting of:

hydrogen;

halogen;

azide;

an R group defined as C1 to C8 alkyl or alkenyl, aryl or heteroaryl optionally further substituted by:

an alkoxy, aryl, heteroaryl or aryloxy group;

-COOH, $-S(O)_2OH$, phosphate, carboxylate or tetrazolyl;

$-S(O)_2OH$, -S(O)OH, -S(O)R, $S(O)_2R$, $-S(O)_2NH_2$, $-S(O)_2OR$, -S(O)OR;

-C(O)R;

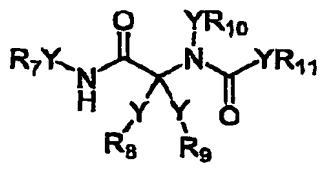
phosphate, carboxylate or tetrazolyl;

an unsubstituted or substituted heterocylic group, wherein the substitution is by:

an alkyl or aryl group, $-CH_2NHC(O)R$, $-CH_2N(C(O)R)_2$, $-CH_2OR$, wherein R is as defined above;

connected to a different R_1 to R_5 to form a new cyclic group;

a substructure based upon a group of the following formula:



II

wherein:

Y is H, R or –C(O)R, wherein R is as defined above;

at least one, but not more than two of R_7 to R_{11} is independently a structure according to formula I; or

a structure comprising a second unit according to formula II linked via a "Y" group wherein each unit is independently substituted by R_7 to R_{10};

with the provisos that:

when R_1 is $-CH_3$, $-S(O)_2OH$ or -H at least one of R_2 to R_5 is not -H or $-S(O)_2OH$;

when a substructure of type II is not present and none of R_1-R_5 form an anhydro bridge, no more than two of R_1-R_5 are $-S(O)_2OH$ and the stereochemistry of I is not gluco or galacto;

2. A compound according to claim 1, wherein said compound is PG2024, PG2037, PG2173, PG2198, as hereinbefore described.

3. A compound according to claim 1, wherein said compound is any one of the compounds of Tables 1-4 of the description.

4. A pharmaceutical or veterinary composition for the prevention or treatment in a mammalian subject of a disorder resulting from angiogenesis, metastasis, inflammation, coagulation, thrombosis, and/or microbial infection, which composition comprises at least one compound according to claim 1 together with a pharmaceutically or veterinarially acceptable carrier or diluent for said at least one compound.

5. The composition according to claim 4 which further includes a pharmaceutically or veterinarially acceptable excipient, buffer, stabiliser, isotonicising agent, preservative or antioxidant.

6. The composition according to claim 4, wherein said compound is present therein as an ester, a free acid or base, a hydrate, or a prodrug.

7. Use of a compound according to claim 1 in the manufacture of a medicament for the prevention or treatment in a mammalian subject of a disorder resulting from angiogenesis, metastasis, inflammation, coagulation, thrombosis, and/or microbial infection.

8. The use according to claim 7, wherein said mammalian subject is a human subject.

9. A method for the prevention or treatment in a mammalian subject of a disorder resulting from angiogenesis, metastasis, inflammation, coagulation, thrombosis, and/or microbial infection, which method comprises administering to the subject an effective amount of at least one compound according to claim 1, or a composition comprising said at least one compound.

10. The method according to claim 9 wherein said mammalian subject is a human subject.

11. The method according to claim 9, wherein said disorder resulting from angiogenesis is a proliferative retinopathy or angiogenesis resulting from the growth of a solid tumour.

12. The method according to claim 9, wherein said disorder resulting from inflammation is rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, allograft rejection or chronic asthma.

13. The method according to claim 9, wherein said disorder resulting from coagulation and/or thrombosis is deep venous thrombosis, pulmonary embolism, thrombotic stroke, peripheral arterial thrombosis, unstable angina or myocardial infarction.

14. The method according to claim 9, wherein said disorder resulting from viral infection is Herpes Simplex.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2004/001800

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. [7]: C07H 5/10, 13/12, 15/04, 11/04, 15/18; A61K 31/70, 31/7012, 31/7016, 31/7028; A61P 7/00, 7/02, 29/00, 35/00, 31/00, 43/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS online, WPIDS: Substructure Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 1985/000973 A1 (AMERICAN CYNAMID COMPANY) 14 March 1985 See whole document especially formulae I and II, claims	1, 3, 4-10, 12, 13
X	US 4459293 (MINER THOMAS G et al) 10 July 1984 See whole document	1, 3, 4-10, 12, 13
X	WO 2003/038054 A2 (NEW YORK UNIVERSITY) 8 May 2003 See structures I–VI	1
X	Derwent Abstract Accession No 2000-100762/09 Class B03 D16 JP 11-315092 (AGENCY OF IND SCI & TECH) 16 November 1999	1, 3, 4

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 March 2005	11 MAR 2005
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized officer O.L. CHAI Telephone No : (02) 6283 2482

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2004/001800

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Derwent Abstract Accession No 2001-337999/36 Class B03 JP 2001048857 (ONO PHARM CO LTD) 20 February 2001	1, 4-10, 14
X	Derwent Abstract Accession No 2000-116716/10 Class B03 WO 1999/065480 (ONO PHARM CO LTD) 23 December 1999 (US 2004/0072767 viewed)	1, 3, 4
X	WO 1993/024506 A1 (ALBERTA RESEARCH COUNCIL) 9 December 1993 See whole document	1, 4-10, 12
X	WO 1997/018222 A2 (GLYCOMED INC) 22 May 1997 See whole document	1, 3, 4-10, 12
X	Derwent Abstract Accession No 96-116981/12 Class B03 WO 1996/003413 (GENYME UK LTD) 8 February 1996	1, 3
X	US 5700918 (HASEGAWA et al) 23 December 1997 See whole document	1, 4-10, 12, 14
P, X	Chemical Abstracts AN 140:314439 & Bytheway, Ian et al, "Validation of Molecular Docking Calculations Involving FGF-1 and FGF-2" Journal of Medicinal Chemistry (2004), 47(7), 1683-1693 See RN 679418-23-6, 679418-24-7	1, 3
P, X	Chemical Abstracts AN 141:54554 & Liu, Ligong et al, "Application of the four-component Ugi condensation for the preparation of sulfated glycoconjugate libraries" Bioorganic & Medicinal Chemistry Letters (2004), 14(9), 2221-2226 See RN 705951-30-0, 705951-31-1, 705951-32-2, 705951-33-3, 705951-34-4, 705951-35-5, 705951-36-6, 705951-37-7, 705951-38-8, 705951-39-9, 705951-40-2, 705951-41-3	1, 3
X	Chemical Abstracts AN 138:82903 & Yoshiizumi, Kazuya et al,"Studies on scavenger receptor inhibitors. Part 1: synthesis and structure-activity relationships of novel derivatives of sulfatides" Bioorganic & Medicinal Chemistry (2002), 10(8), 2445-2460 See RN 485323-47-5	1, 3, 4
X	Chemical Abstracts AN 133:267051 & Faroux-Corlay, B. et al, "Synthesis of single- and double-chain fluorocarbon and hydrocarbon galactosyl amphiphiles and their anti-HIV-1 activity" Carbohydrate Research (2000), 327(3), 223-260 See RN 298712-98-8	1, 3, 4
X	Chemical Abstracts AN 131:322848 & Sakagami, Masahiro et al, "Syntheses and evaluation of biantennary oligosaccharide ligands mimicking Sialyl Lewis X" Chemical & Pharmaceutical Bulletin (1999), 47(9), 1237-1245 See RN 167016-70-8	1, 4-10, 12

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2004/001800

C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Chemical Abstracts AN 129:107414 & Mulligan, Michael S. et al, "In vitro and in vivo selectin-blocking activities of sulfated lipids and sulfated sialyl compounds" International Immunology (1998), 10(5), 569-575 See RN 209860-41-3	1, 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2004/001800

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: **1, 3 (in part)**
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
See supplemental box

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Supplemental Box
(To be used when the space in any of Boxes I to VIII is not sufficient)

Continuation of Box No: II

The permutations and combinations of the various variables of the structural formula I of claim 1 give many classes of compounds that the specification does not provide support for. The claim is also drafted so unclearly that the scope of the claim cannot be determined. Attempts have been made to conduct a search of the compounds covered by claim 3. It was economically not possible to retrieve all related documents due to the large number of closely related compounds from the substructure searches. Only a selection of the prior art has been cited in Box C.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/AU2004/001800

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
WO	1985/000973	EP	0153393	US	4515782		
US	4459293	US	4404365				
WO	2003/038054						
JP	99315092						
JP	2001048857						
WO	1999/065480	AU	41665/99	EP	1095653	US	2004/0072767
WO	1993/024506	CA	2110386	CA	2110495	CA	2110582
		CA	2110707	CA	2110997	CA	2118405
		CA	2118522	EP	0588848	EP	0588852
		EP	0589933	EP	0589951	EP	0591254
		EP	0591256	EP	0643718	EP	0650492
		US	5352670	US	5374655	US	5550155
		US	5580858	US	5646123	US	5759993
		US	5872096	US	5882901	US	5939290
		WO	1992/022301	WO	1992/022563	WO	1992/022564
		WO	1992/022565	WO	1992/022661	WO	1992/022662
		WO	1993/024505				
WO	1997/018222	AU	11228/97	US	5874411		
WO	1996/003413	AU	32236/95	CA	2194492	EP	0772618
		US	5874548				
US	5700918	WO	1995/026970				

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

END OF ANNEX